Exploring the biopsychosocial landscape of chronic illness: A case study of systemic lupus erythematosus (SLE) from epigenetics to education

by

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The following served on the Examining Committee for this thesis. The decision of the Examining Committee is by majority vote.

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

Exceptions to sole authorship:

Chapter 3:

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I hereby declare that as lead author on all three manuscripts, I was responsible for all stages of study conceptualization, data collection and analysis. I was responsible for drafting all manuscripts herein, and submitting all articles for publication in the respective peer-reviewed journals. I addressed all comments from peer reviewers. Dr. Susan Elliott, as the primary supervisor, provided significant direction and editorial assistance. All other co-authors advised on data collection, analysis and interpretation of results, and provided feedback on draft manuscripts.

Abstract

Systemic lupus erythematosus (SLE), or lupus, is a chronic autoimmune condition and global public health issue. SLE is uniquely characterized as gendered, racialized, episodic, invisible and idiosyncratic. SLE primarily impacts women, and most severely, women of colour. Cardiovascular disease (CVD) is a main driver of morbidity and mortality among SLE populations. Recent literature has begun to characterize both SLE and CVD as "biopsychosocial" and concomitant with place. However, the complex biological-social interplay influencing SLE disease trajectories, and morbidity and mortality from CVD in SLE, is not well understood.

This thesis explores the biopsychosocial landscape of SLE with three main objectives: 1) to assess theoretical and methodological support for social epigenetics studies of SLE; 2) to investigate existing literature around social factors influencing the development of CVD in SLE; and 3) to engage knowledge users in the co-production of educational tools about the risks of CVD in SLE. Drawing on health geographical approaches, ecosocial and biopsychosocial theories, and feminist perspectives, a multimethods research design was employed involving narrative review, scoping review, focus groups, and interviews. This transdisciplinary process was supported by an embedded integrated knowledge translation (iKT) approach that included knowledge users as equal partners.

This research positions social epigenetics as a novel and transdisciplinary line of inquiry to understand the development and trajectories of chronic diseases. While some theoretical and methodological support exists - with respect to ecosocial and lifecourse theories, and epigenome-wide association studies and exposomic approaches, respectively - expansion in both of these areas is needed with particular attention to intersectionality. Building on this theoretical foundation, and using SLE as a case study, the scoping review revealed several social factors

demonstrated to be central to CVD in SLE populations: socioeconomic status, race, mental health, and gender. These results, and complementary information about CVD specific to SLE, were mobilized through the co-development of a lay language patient education resource. Through a focus group with key informants and interviews with patients, knowledge users advised on tailoring content, format, accessibility and inclusivity for the SLE community, with the ultimate goal of improving patient knowledge about CVD.

This body of work makes theoretical contributions to the practical application of social epigenetics studies, integrating intersectional perspectives, and bridging basic and social science conceptualizations of health and ill-health. Methodologically, these studies contribute to the study of iKT frameworks and patient engagement in the context of chronic illness. This research collectively adds to our substantive understanding of SLE through a biopsychosocial lens, and the risk landscape of CVD in place. With respect to healthcare policy and practice, the findings herein may provide future targets for CVD risk assessment and prevention in the SLE context, inform educational and social interventions to support SLE treatment, and contribute to the development of a future patient-led research agenda for SLE in Canada.

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Dedication

This work is dedicated to my parents, who have inspired, encouraged and led by example a lifelong love of learning.

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CHAPTER ONE

INTRODUCTION

1.1 Research problem

Chronic autoimmune diseases are a rapidly increasing global public health concern. Recent studies indicate that up to 10% of the global population currently live with one or more immune-mediated illnesses, with prevalence increasing over the past two decades (Conrad et al., 2023). While autoimmune diseases can be treated, they generally cannot be cured, and patients' continued reliance on healthcare systems and supports accrues significant economic costs at a variety of scales (CDC, 2023). The impacts of illness also have a multitude of "lifecosts" (Dixon et al., 2022) for the individual, as symptoms can have wide-ranging physical, mental, and economic consequences, imposing a detrimental impact on quality of life (Pereira et al., 2020). As the burden of autoimmune diseases continues to grow, stark health inequities have been revealed with respect to etiology, experiences, and outcomes.

1.1.1 Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE), commonly known as lupus, is a chronic autoimmune condition in which the immune system becomes dysregulated, leading to ongoing inflammation in the body. One of the primary drivers of SLE are autoantibodies, or antibodies generated against self (Ameer et al., 2023). While antibodies normally protect against infection, these autoantibodies begin to attack normally healthy organs and tissues. Over time, these organs and tissues become damaged, impairing homeostatic processes and leading to symptoms such as fever, extreme fatigue, muscle/joint swelling and/or pain, lung and kidney issues, UV sensitivity,

and skin rash, including a characteristic butterfly-shaped rash on the face called malar rash (Lupus Research Alliance, 2023). In some cases, SLE can present with neuropsychiatric symptoms such as depression and other mental disorders, or cognitive dysfunction and "brain fog" (Carrión-Barberà et al., 2021; Mackay, 2015).

Clinical signs and experiences of SLE are highly variable from person to person and can be mild to severe. Because of this high variability, SLE has been referred to as the "disease of 1000 faces" (Bernatsky & Senecal, 2004). SLE-related illness follows a wax and wane trajectory, in which periods of increased symptom severity, called "flares", are interspersed with periods of remission (Fernandez & Kirou, 2016). Although the etiology of SLE remains unclear, it appears to arise through a complex combination of genetic predispositions and exposures to environmental influences. Because of the intricate interplay of biological, psychological, and social systems in SLE, scholars have begun to conceptualize it as "bio(psycho)social" (Dixon et al., 2022; Kinsey et al., 2018).

The prevalence of SLE varies spatially, as well as with respect to particular social groups. In Canada, 1 in 2000 people are affected by SLE, and emerging studies indicate that this number is increasing (Bernatsky et al., 2007; Fatoye, Gebrye, & Svenson, 2018). Between the years 2000 and 2015, the prevalence of SLE in the province of Alberta nearly doubled (Fatoye et al., 2018). Similar trends have been seen in the United States, although incidence rates remain relatively stable (Li et al., 2020). Both incidence and prevalence of SLE are highly variable across European regions, with some countries such as Denmark (Hermansen et al., 2016) and France (Arnaud et al., 2014) reporting lower rates than North America, and a notably high prevalence in Crete, Greece (Gergianaki et al., 2017). Studies from the Asia Pacific region are similarly variable, with notably high incidence and prevalence rates across Taiwan and China compared to

other countries such as Australia, Korea and Singapore (Tanaka et al., 2022). Studies from the global South are less robust, but do confirm the presence of SLE and indicate similar epidemiological patterns. Taken together, this evidence corroborates that SLE is indeed, a global health issue (Barber et al., 2021).

The epidemiology of SLE reveals striking social disparities. 90% of patients with SLE are women (Izmirly et al., 2021; 2017), and racialized groups including Black, Indigenous, Hispanic and Asian women are disproportionately represented. Black women are twice as likely to be diagnosed with SLE as white women, and they tend to be diagnosed with more severe disease at earlier ages (Lim et al., 2014; Somers & Richardson, 2014). Similar trends are seen among Indigenous women across the US (Ferucci et al., 2014) and Canada (Barnabe et al., 2012). These populations also have significantly worse health outcomes; for example, Black women experience severe disease manifestations such as renal disease at a two-fold rate compared to their white counterparts (Somers et al., 2014), and Black race has been reported as an indicator of reduced ten-year survival (Merola et al., 2014). In addition, increased SLE disease activity, morbidity and mortality have all been associated with low socioeconomic status (SES) and fewer years of education (Hasan, Fike, & Hasni, 2022; McCormick et al., 2020). Among all young women, data from the US indicates that SLE is a leading and underrecognized cause of death (Yen & Singh, 2018).

While many of the symptoms of SLE are invisible, or not outwardly seen by others, they can have debilitating impacts on many aspects of wellbeing. The physical symptoms of SLE can be painful and sometimes incapacitating, hindering the performance of daily activities related to work, childcare, household chores, volunteering and leisure (Dixon et al., 2022). Following diagnosis, individuals are forced to change many of their routines and "life habits" (Aim et al.,

2022). These life changes often precipitate a change in self-identity that patients must then negotiate and navigate on top of their symptoms and being ill (Sutanto et al., 2013a).

Many patients with SLE report experiencing cognitive dysfunction, including "brain fog", and mental illnesses such as depression and anxiety are encountered at high rates in the SLE population (Moustafa et al., 2020; Zhang et al., 2017). These effects may be attributed to the physical or psychosocial impacts of SLE, a side-effect of treatment, or the direct impacts of disease pathogenesis.

A frequently recounted challenge for patients with SLE is the changing dynamics in their social networks. Given the invisible nature of their symptoms, patients voice that family, friends, colleagues, and sometimes even health professionals do not understand their illness (Sloan et al., 2021; Sutanto et al., 2013a). Others report fearing and facing stigma and discrimination upon disclosing their illness to others (Aim et al., 2019). In the workplace, people with SLE may at times be unable to perform their regular activities due to feeling unwell, SLE-related disability, or needing to travel to healthcare appointments, forcing many to choose unpaid time away from work, or change their career trajectories altogether to part-time or non-employment (Dixon et al., 2022). In addition to this lost income, patients with SLE incur substantial illness-related costs, including but not limited to expensive treatments, complementary healthcare, travel to and from healthcare appointments, and childcare (Barber & Clarke, 2017). While all patients with SLE have unique experiences and face different "lifecosts" – the direct and indirect economic and other costs (Dixon et al., 2022) – these individuals consistently report a significantly decreased overall quality of life (Gomez et al., 2021; Wang et al., 2019).

Taken together, we characterize SLE as a condition which is uniquely gendered, racialized, episodic, idiosyncratic, and invisible, with wide-ranging impacts on all facets of life.

1.1.2 Risks of cardiovascular disease in SLE

In recent decades, treatment advances have made it possible for patients with SLE to live longer. However, this is not without consequences; patients with SLE are now more at risk for developing a number of co-morbidities, including infectious and chronic diseases, as they age through this extended lifecourse (Arnaud & Tektonidou, 2020).

One illustrative example is cardiovascular disease (CVD), which is currently a main driver of SLE morbidity and mortality (Barber et al., 2021). As an umbrella term for all disorders of the circulatory system, CVD encompasses a number of conditions including heart attack, heart failure, coronary artery disease, thrombosis, embolism and stroke (WHO, 2023). Like other chronic diseases, the causality of CVD is complex and multifactorial, developing over the life course. Risk of CVD in the general population has been associated with a number of biological and metabolic factors (e.g., genetic predisposition, lipids, blood pressure) and health-related behaviours (e.g. smoking, diet, alcohol use, physical activity) (Yusuf et al., 2020). While some of these factors are intrinsic and cannot be changed (i.e., genetics), many can be mitigated by lifestyle interventions. A recent report indicates that as much as 70% of CVD is due to modifiable risk factors (Yusuf et al., 2020). Despite ongoing efforts by advocacy and public health organizations, CVD risk factors – especially those that are modifiable – continue to disproportionately impact populations that are racialized, low-SES, low education, and facing other health inequities (Wenger et al., 2022).

Although CVD has been relatively widely-researched and is a prominent fixture of public health initiatives, much of the existing research has focused primarily on men (Dougherty, 2011; Jin et al., 2020). This marks a significant shortcoming in clinical research, as an emerging body of evidence indicates that CVD operates much differently in women; it manifests in different

conditions, presents with different symptoms, and a number of female-specific risk factors have been identified related to hormonal conditions and pregnancy which are not routinely involved in preventative and diagnostic tools (Geraghty et al., 2021; O'Kelly et al., 2022). Women more frequently adopt protective health-related behaviours, but less frequently receive healthcare follow up, cardiac investigation, and treatment (Walli-Attaei et al., 2020). These compounding concerns have led the American Heart Association to issue a global call to action to reduce the risks and burden of CVD in women by promoting health equity through collective education, advocacy, optimized clinical care and community engagement (Wenger et al., 2022). Discussions of gender inequities in CVD risk are particularly pertinent in the context of SLE, wherein the vast majority of patients are women.

Patients with SLE are at significantly increased risk of CVD compared to the general population. In Bernatsky et al.'s (2006) multi-center international cohort study of SLE, 313 of 1,255 fatalities (25%) were attributed to CVD, and the risk of a CVD-associated event was greatest in the first year following diagnosis. A Canadian cohort study by Antonio et al. (2017) found that patients with SLE were, on average, more than twice as likely to experience myocardial infarction, stroke, and other CVD events compared to age and sex-matched controls.

While certain risk factors such as age, smoking and obesity have been shown to be important in the development of CVD for individuals with SLE, this population also faces additional risks due to ongoing inflammation, immune dysregulation, and prolonged treatment with corticosteroids (Lu et al., 2021). SLE disease activity and associated tissue damage has also been strongly implicated in this process (Frostegård, 2023). While there have been calls for improved screening and detection practices among this group, current risk prediction models do not account for SLE-specific factors, and thus perform poorly in this context (Sivakumaran et al.,

2021). Taken together with existing social disparities in SLE, the compounding dangers of CVD coalesce to place additional risk on an already vulnerable population.

SLE and CVD are both complex chronic diseases characterized and shaped by social disparities. In SLE populations, these two conditions act synergistically to impact the health trajectories of already vulnerable equity-seeking populations. Women, people of colour, lower income and lower education individuals are consistently at greater risk of both SLE and CVD, and experience more severe disease outcomes (Barber et al., 2023; Javed et al., 2022; Wenger et al., 2022). These stark inequities indicate the importance of social and environmental stressors, in combination with genetic predispositions, in spurring SLE and CVD-related physiological processes (Kinsey et al., 2018). Despite these disproportionate risks and impacts, the interplay between SLE biology, CVD risk, and socio-environmental context remains understudied.

With respect to the latter, recent research evidence points to the importance of the exposome and social epigenetics.

1.1.3 The Exposome

The exposome was first proposed by Wild (2005) to describe the total accumulation of exposures for a particular individual over the lifecourse. The exposome comes in response to the concept of the genome, or the totality of genetic material in a particular organism, and encompasses all physical, social, and environmental interactions from conception to death. Wild (2012) divided these exposures into three broad categories: the general external environment (e.g. geographic region, social systems, stress), specific external environment (e.g. health behaviours, chemical contaminants, infections), and internal environment (e.g. microbiome, inflammation). The resulting exposome is both dynamic and cumulative, continually changing

through space and time. In line with lifecourse theory, the exposome also accounts for particularly sensitive periods in which exposures may be disproportionately impactful, such as *in utero* and during early childhood development (Wild, 2012). In the context of chronic disease, understanding exposures through the exposome has been theorized as a way to understand who develops disease, and when.

The multitude of exposures captured by the exposome are necessarily linked with place, as well as an individuals' movements through space and time. Recognizing this, geographers are expanding methodological approaches to measuring individual and population exposomes using geographic information systems (GIS) and other geospatial technologies. For example, ecological momentary assessment (EMA) uses smartphones or other wearable mobile trackers to collect data on movements, behaviours, and where and when they take place (Stahler, Mennis, & Baron, 2013). This allows researchers to collect high-resolution data on all exposures encountered while wearing the technology. Geospatial data is then merged with hazard monitoring and/or biomarker assessment to develop the exposome profile.

Exposomic approaches have been critiqued for a number of reasons. First, while conceptually interesting, it is near impossible to track individuals for the entirety of the lifecourse, making inferences about health trajectories difficult. Studies employing these methodologies have found a high level of variability across individuals' exposomes; even those in close geographic proximity can have vastly different profiles (Jiang et al., 2018). Currently, much exposure data is not predictably linked with specific chronic health outcomes, in part due to their complex etiologies (Jacquez, Sabel, & Shi, 2015). Other methodological questions have been raised with regards to accounting for critical and sensitive periods during the lifecourse (Pearce, 2018) and the need for a standardized approach to exposome study design and analysis

(Hu et al., 2022). It has also been suggested that exposomic approaches may be individualized, and thus draw attention away from critical health inequities (Prior, Manley, & Sabel, 2019).

Despite these challenges, geographers and other health-related researchers have begun to initiate exposomic analyses related to diabetes (Misra & Misra, 2020), mental disorders (Erzin & Gülöksüz, 2021), and maternal and child health (Maitre et al., 2018; Robinson et al., 2018). Recently, scholars have advocated for this approach for unravelling the complex gene-environment interactions in SLE (Baisya, 2023; Leffers et al., 2019). The European-based EXIMIOUS consortium is beginning to fill this gap with a large-scale, multi-year, multi-disciplinary study investigating connections between the exposome and the "immunonome" in a variety of autoimmune and inflammatory conditions, including SLE (Ronsmans et al., 2022). Researchers aim to use bioinformatics and systemics immunology to provide insight into how the exposome impacts inflammatory processes; however, the study remains in early stages and findings have not yet been released.

1.1.4 Social epigenetics

While genetics are a contributing factor to the development of many chronic diseases, epigenetics have more recently been proposed as an additional potential mechanism. The term "epigenetics" refers to the molecular alterations made to DNA in response to an organism's environment that direct the production of cellular proteins (Cunliffe, 2016). Depending on the environmental conditions, epigenetic markers may turn genes off (i.e. decreased or halt expression of proteins) or turn genes on (i.e. increased expression of proteins). Epigenetic changes thereby change the structure and/or function of cells, and in turn, alter tissue and organ systems to adapt to environmental stimuli. Scaling up to the population level, similar epigenetic patterns would be expected among individuals who are subjected to similar environmental

conditions. A key characteristic of epigenetics is that modifications can be heritable, imprinting subsequent generations (Cunliffe, 2015).

Decades of studies on the social determinants of health have linked a number of socioenvironmental factors to the development and outcomes of chronic disease. The social determinants of health refer to non-medical factors that influence health outcomes, including income, education, housing, employment, and discrimination, among others (Wilkinson & Marmot, 2003). Building on this foundational concept, the term "social epigenetics" refers to the molecular alterations made to DNA in response to an organism's *social* environment. As epigenetic patterns may translate to health outcomes, epigenetic patterns instilled by social context may reveal a mechanism for how social conditions are embodied, and further provide an explanation for social health inequities (Martin et al., 2022).

Although social epigenetics has only been conceptualized fairly recently, initial studies has provided compelling evidence for social epigenetics as a pathway linking to chronic disease. One of the first and most prominent examples is a study of the intergenerational impacts of famine during the Dutch Hunger Winter, occurring in 1944-45. Heijmans et al. (2008) found individuals who were *in utero* during the famine had decreased methylation of the *IGF2* gene. Further studies have associated this particular epigenetic mark with the development of schizophrenia (Harrison, Freemantle, & Geddes, 2003; Pidsley, Dempster, & Mill, 2010). Similar studies have detected epigenetic patterns among individuals who underwent stressful experiences in early childhood (e.g. Essex et al., 2013; Powell et al., 2013), or who grew up in lower SES households (Miller et al., 2009).

Epigenetic mechanisms have similarly been demonstrated to be an important mechanism in SLE; a number of specific epigenetic changes have been linked to the dysregulation of the

immune system and subsequent autoimmunity observed in SLE patients (reviewed Wu, Chang, & Lu, 2020). It has been posited that exposures to environmental contaminants, pollution, infectious agents, or even diet may mediate these epigenetic changes (Montoya et al., 2023; Woo et al., 2022). Although there is much evidence to support the role of epigenetics in mediating SLE-related disease, this line of study has not substantially considered the role of social systems and the coinciding social determinants of health in mediating these patterns.

1.2 Research goal and objectives

Informed by the above, the goal of this research is to explore the biopsychosocial landscape of systemic lupus erythematosus (SLE). To this end, a multimethods approach was employed to meet three specific research objectives:

1) To assess theoretical and methodological support for social epigenetics studies of SLE;
2) To systematically investigate the existing literature around the known social factors influencing the development of CVD among people with SLE;
3) To engage knowledge users in the co-production of knowledge translation tools to educate patients with SLE about the risks of CVD.

1.3 The chronic disease, health and place nexus

Chronic diseases are the leading cause of morbidity and mortality globally (WHO, 2022). In Canada, nearly half of the population (44%) is living with one or more chronic conditions, with the most common being cardiovascular diseases (e.g. hypertension, ischemic heart disease), chronic respiratory diseases (e.g. chronic obstructive pulmonary disorder (COPD), asthma), cancer, and diabetes (Government of Canada, 2019). Chronic diseases are generally

characterized by a sustained period of illness, which may be accompanied by an associated impairment or disability (Vineis, 2018). In contrast to infectious diseases, chronic diseases are not passed from person to person; rather, chronic diseases arise over the lifecourse, usually as a result of complex genetic and environmental interactions (Ben-Shlomo & Kuh, 2002). Therefore, chronic diseases cannot be prevented by vaccines, and while they can be treated, cannot be cured (Vineis, 2018). In addition to the main classes of chronic diseases illustrated above, a number of other conditions are becoming recognized as meeting these criteria, including mental illness, allergy, and autoimmune conditions (Shantz & Elliott, 2020).

Like all states of health and wellbeing, chronic diseases are inextricably linked with place. In human geography, "place" is defined as a location imbued with meaning. Places are in a constant state of "becoming", or being constructed and re-constructed as an "ongoing assemblage" of people, environments, and other elements (e.g. physical/natural or built), as they coalesce with cultural and subjective meaning (Gregory et al., 2009). Thus, place encapsulates all the ever-changing aspects of a location, including the physical settings as well as the ongoing systems, relationships and experiences within them.

The etiology of chronic disease unfolds in place, and as a result of place-based influences. Although the developmental origins are complex and in many cases, not well understood, current evidence indicates that many chronic diseases arise as a result of genetic predisposition combined with environmental factors (Vineis, 2018). Such factors may be physical/chemical, psychosocial, or built, and can have direct impacts on the body, or may function indirectly, such as through promoting health behaviours (e.g. substance use) or mediating chronic stress (e.g. systemic racism).

For example, exposure to ambient air pollution is associated with increased incidence of diabetes, hypertension, stroke, myocardial infarction and asthma (Karimi et al., 2020), as well as autoimmune diseases (Bernatsky et al., 2015). At the neighbourhood level, communities with low socioeconomic status and/or poor infrastructure consistently report higher rates of chronic diseases (Kim et al., 2018; Rachele, Giles-Corti, & Turrell, 2016). In such neighbourhoods, access to resources such as healthcare (Shah, Bell, & Wilson, 2016), green space (Cohen et al., 2012), and nutritious food outlets (Stevenson et al., 2019) are often limited, and inhabitants experience barriers to physical activities such as walking (Frank et al., 2022); conversely, substances such as tobacco (Pearce, Barnett, & Moon, 2012) and alcohol (Matheson et al., 2012) are more accessible and are used more regularly, all leading to heightened risk of developing chronic conditions.

At the individual level, the social environment mediates risk of chronic disease via systemic discrimination and traumatic life experiences which instigate acute and/or chronic stress. For example, multiple pathways of structural racism have been implicated in the high incidence of chronic diseases among Canadian First Nations communities (Stelkia, 2023), and stressful life events have been associated with diabetes, cardiovascular disease, and mental disorders in a number of contexts (Pearlin et al., 2005; Renzaho et al., 2013). One specific example of this is a recent study by Miller-Archie et al. (2020), which found that individuals who were directly exposed to the events and aftermath of the September 11, 2001 terrorist attack in the US, and who developed post-traumatic stress disorder (PTSD) as a result, had nearly 3-fold risk of developing systemic autoimmune disease.

In addition to developing as a result of place, chronic diseases are also experienced *in* place. Life with a chronic disease and the impacts of being unwell, in many cases, force

individuals to interact differently with their environments than before they were ill. For example, Crooks and Chouinard (2006) detail how women negotiate their chronically ill identities in places such as healthcare clinics, work and home. Being chronically ill, healthcare clinics became more important and frequently visited places, and while in them, women embodied their "ill" self. In contrast, women at work and home described presenting a "healthier" self, often finding themselves needing to explain – and justify – the invisible nature of their symptoms to family and friends. These relational constructions of self within place illustrate the liminal spaces of chronic disease where individuals may be healthy one day and ill the next, or sometimes both healthy and ill simultaneously. Similar research reveals that places are also (re)produced in the context of experiencing chronic disease. For instance, several studies have described the "shrinking lifeworlds" of chronically ill women (Crooks, 2007; Dyck, 1995). As womens' bodies, abilities, and daily activities change as a result of their disease, their interactions with places and people gradually reduce. Thus, not only does place impact experiences of chronic disease, but chronic disease also impacts experiences of place.

Many of these intersections between health, place and chronic disease are reflected in systemic lupus erythematosus (SLE). While SLE is substantively linked with several genetic components (Mohan & Putterman, 2015), evidence suggests that place-based influences are equally central to SLE etiology. Consistent environmental exposures to substances like silica, UV light, solvents, air pollution, infectious agents and other contaminants over time have been connected to the development of SLE, usually occurring through work or leisure activities (Cooper et al., 2010) or in urban environments (Finckh et al., 2006). In addition, SLE health trajectories have been shown to be negatively affected by perceptions and experiences of racial discrimination (Chae et al., 2015). Over time, repeated exposures to such physical and/or social

stressors trigger inflammatory pathways, epigenetic changes, and autoimmune responses characteristic of the disease (Parks et al., 2017). Even after treatment, these types of stressors continue to cause disease flares (Fernandez & Kirou, 2016). Following an SLE diagnosis, patients report changing place-based experiences: similar to the work by Dyck, Crooks and Chouinard (1995; 2006; 2007), places like home and healthcare clinics become more central, while due to the physical and mental impacts of SLE, social relationships rearrange, often resulting in greater isolation (Petrocchi et al., 2022; Sutanto et al., 2013). For many, the onset of SLE and related disabilities may instigate a change in career, therefore altering experiences of the workplace (Dixon et al., 2022). Taken together, this evidence reveals that SLE develops in place, is experienced in place, and influences experiences of place.

1.4 Research context

This research takes place in Canada. While Manuscript #3 expressly draws upon Canadian participants and produces resources tailored for the Canadian context, Manuscripts #1 and #2 take a more global focus. Despite these more generalized approaches, I situate these studies in the Canadian context in acknowledgement that my positionality as a Canadian researcher, and partnerships with Canadian knowledge users, influence all aspects of the research processes herein.

Canada was chosen as the geographical setting for these studies for several reasons. First, 1 in 2000 Canadians are living with SLE, and preliminary evidence indicates that this number is increasing (Fatoye et al., 2018). Based on the current population, this translates to over 38,000 patients with SLE in Canada (Statistics Canada, 2023). In addition to those directly affected (i.e., receive an SLE diagnosis), many more are indirectly affected (i.e., daily lives impacted by SLE),

including family members and children of those with SLE, care takers, and healthcare professionals. The average medical costs for a single SLE patient in Canada have been estimated at $10,608 per year (Clarke et al., 2015). These costs were even higher for patients with severe SLE, totalling $15,048 annually (Clarke et al., 2015). Based on these estimates, healthcare for patients with SLE costs over three times more than the general population (Fatoye et al., 2018). These costs therefore have important economic implications for the publicly funded Canadian healthcare system. Taken together, research on SLE etiology, diagnosis and management stands to both improve quality of life for those affected at the individual level, but scaling up, may also have significant economic impacts nationally.

In addition to the multitude of SLE-related impacts that required urgent attention, Canada also provides a unique geographic context for investigation. Canada has a universal healthcare system that is publicly funded, and allows all Canadians access to hospitals and physicians free of personal costs (Government of Canada, 2023). This overarching system is divided geographically, with each province or territory responsible for implementing, organizing and delivering healthcare services. Each provincial/territorial government has decision-making power over the management of their healthcare systems, in line with *The Canada Health Act* (Government of Canada, 2023). Despite the "universal" title, there is an unequal spatial distribution of healthcare resources, with higher concentrations often found in urban rather than rural centers, and variability even within urban centers across neighbourhoods (Shah et al., 2016). As a result, the availability and access of healthcare, specialists, and treatments is geographically uneven and highly place-based.

The SLE research landscape in SLE is decidedly active, with clinicians and other researchers collaborating through lupus clinics and institutes across the country. Canadian researchers have

engaged in a number of landmark SLE cohort studies through the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) (Gladman et al., 1996; Petri et al., 2012; Urowitz et al., 2007). This is further supported by a number of national advocacy groups such as Lupus Canada (www.lupuscanada.org), and provincial groups including Lupus Ontario, Lupus Society of Alberta, and others. While many provinces and territories do have specialized SLE organizations, their activity can be variable and intermittent, in part due to the cyclical health and illness of the affected individuals who run them.

To achieve an SLE diagnosis in Canada, patients must first visit their primary care physicians, or in some cases, may be diagnosed in hospital. Based on the symptoms presented, primary care physicians may order laboratory-based testing or refer to secondary (e.g. specialists such as rheumatologists or dermatologists) or tertiary healthcare (e.g. advanced procedures) as necessary (Government of Canada, 2023). There is no single definitive test for SLE; diagnoses are made based on a combination of medical history, physical exams, bloodwork, and the presence of anti-nuclear antibodies (ANA), which are a biomarker found in 95% of patients with SLE (Fanouriakis et al., 2021). The generalized, variable and invisible nature of SLE symptoms, in combination with a documented lack of awareness among general practitioners (Sawah et al., 2015), can make obtaining an SLE diagnosis challenging. The average time from first symptoms to diagnosis for an SLE patient is 5.6 years (Sawah et al., 2015). Patients see an average of three healthcare providers before receiving an SLE diagnosis, and 62.8% report being misdiagnosed prior (Sawah et al., 2015). It is important to note that these numbers come from a survey of English-speakers who are predominantly white, and likely under-represent the challenges experienced by immigrants, racialized groups, and people with disabilities.

Upon diagnosis, patients with SLE are commonly treated with immunosuppressive drugs such as steroids, and/or antimalarials such as hydroxychloroquine (commercially known as Plaquenil) (Keeling et al., 2018). While effective, these medications can have mild to severe side effects, sometimes affecting patient compliance (Hardy et al., 2021). Based on SLE-related damage, patients may be prescribed additional medications, for example to improve kidney function or reduce CVD risk (Ameer et al., 2022). This remained the status quo until 2011, when Health Canada approved belumimab (Benlysta), the first new lupus-specific drug in 50 years (Navarra et al., 2011). More recently, Canadian researchers have developed a drug for lupus nephritis called voclosporin (Lupkynis) (Rovin et al., 2021). Despite approval for use by the United States Food and Drug Administration in 2021, voclosporin is not yet available for widespread use in Canada (Heo, 2021). While individual or provincial healthcare systems absorb some of the costs for these prescriptions, many patients have partial coverage, or rapidly exceed insurance maximums, and are left paying out of pocket for life-saving medications (Dixon et al., 2022). Complementary care treatments such as physiotherapy, massage, counselling, etc., that are often required by patients with SLE are generally not covered by provincial health plans, thus incurring additional financial costs (Dixon et al., 2022; Moore et al., 2000).

In line with evidence from other regions, and as described above, the epidemiology of SLE in Canada varies according to age, sex, and race/ethnicity. The overall incidence of SLE in Canada is 4.43 per 100,000 population (Fatoye et al., 2018) and peaks between ages 45-64 (Borchers et al., 2010). Between 2000-2016, incidence was measured at six times greater for women than for men (Fatoye et al., 2018). Overall incidence rates in Canada have remained stable over time, though emerging evidence from Alberta indicates that prevalence is increasing. Prevalence estimates of 47.99 per 100,000 people nearly doubled to 90 per 100,000 people in 2015 (Fatoye

et al., 2018). At the same time, mortality due to SLE in Canada has decreased over time, likely reflecting the improved detection and treatment context (Tselios et al., 2019).

Canadian Indigenous populations are at particularly high risk for SLE; one study conducted in Manitoba demonstrated that prevalence in these groups is nearly twice that of those non-Indigenous (Peschken & Esdaile, 2000) and similar findings were reported among First Nations populations in Alberta (Barnabe et al., 2012). While a fulsome spatial analysis of SLE epidemiology has not been conducted in Canada, some evidence positions Toronto, Ontario as a "lupus hot spot" (Al-Maini et al., 2013). Within Toronto, spatial modelling has identified one particular neighbourhood with a disproportionate amount of cases; notable characteristics of this area include Wellesley Hospital, the location of a one-time lupus clinic, and a high rate of violent crime (Li et al., 2012). However, it's also possible that other social and structural determinants that were not included in the analysis (e.g., SES, race/ethnicity, infrastructure, chemical contaminants) might contribute to this geographical pattern. It also remains unclear as to whether such places influence the development of SLE, or whether those with SLE or related health issues rather cluster around urban regions with more specialized healthcare resources.

1.5 Dissertation outline

This dissertation is presented as a collection of three manuscripts. While each manuscript contributes to an overall research agenda, each study asks unique research questions and consequently employs different methodologies.

Following this introduction, Chapter 2 provides an overview of the methodology, including the research design, theoretical framing, and research techniques. Chapter 3 addresses the first research objective and discusses the theoretical and methodological foundation for

conducting social epigenetics studies. This manuscript has been published in *Health & Place.* Chapter 4 addresses the second research objective and describes the findings of a scoping review investigating the social factors influencing the development of CVD in SLE. Chapter 5 addresses objective three and presents a qualitative study of the co-production of patient education resources. Together, Chapters 3-5 form the substantive basis of the dissertation. Chapter 6 provides a discussion of the key findings in the context of the broader literature, including the theoretical, methodological and substantive contributions of this dissertation, as well as limitations and opportunities for future research. Additional information (e.g. data collection tools) can be found in the Appendices.

CHAPTER TWO

METHODS

2.1 Approaches to research in health geography

Health geography is a sub-discipline of human geography focusing on the relationships between humans and their environments in the context of health and wellbeing (Gatrell & Elliott, 2014). Health geographers operationalize foundational geographical principles to explore how health and ill-health are constructed spatially and temporally, in place, at a variety of scales. Research in this field is differentiated from other health-related disciplines by a primary focus on the foundational geographical concepts of space, place, and scale as they relate to a variety of health issues. Also integral to health geography research is the encompassing of multiple methodologies (e.g. qualitative, quantitative, mixed methods, among others) as well as critical perspectives and an emphasis on interrogating health inequities. A major component of health geographical approaches, and foundational to health geographical studies, are the grounded integration and development of theory to support the investigation of complex health issues. As the social epidemiologist Nancy Krieger has stated, "without theory, observation is blind and explanation impossible" (Krieger, 2011b). Theory in health geography – as opposed to other disciplines, namely the basic sciences – refers to a lens for observation that researchers employ in generating their research questions, throughout the study, and in interpreting research results. An explicit engagement with theory therefore ensures that researchers avoid asking poorly conceived questions or produce inaccurate or irrelevant results (Krieger, 2011a). Applying a theoretical framework also assists in identifying what is missing from an analysis, and allows researchers to connect findings back to the broader context (Krieger, 2011b).

Since the discipline emerged in the 1990s, health geographers have adopted and contributed to the development of a wide range of theories. These theoretical perspectives vary in their ontological (i.e. "what we can know") and epistemological (i.e. "how we know") underpinnings, but function in tandem to build holistic views of health and ill-health (Castree, Rogers, & Sherman, 2005). Common theoretical perspectives in health geography include positivism, social constructionism, structuralism, and structuration, for example (Gatrell & Elliott, 2014). While positivist approaches rely on quantitative or otherwise observationally-acquired evidence to uncover a single universal knowledge or truth, social constructionists see knowledge or truth as collaboratively shaped by groups of people with iterative and shared meanings (Gatrell & Elliott, 2014). Structuralism, in contrast, focuses on how social structures dictate human experience, while structuration gives more equal consideration to both structures and human agency (Gatrell & Elliott, 2014).

One particular theoretical area that health geographers have engaged with is feminist perspectives. Drawing upon the work of primarily Black feminist scholars centring gender in social research, geographers have expanded these views to consider gender roles as produced in place (Dyck, 2003; Stafford et al., 2005). Building upon this work, health geographers have also theorized the body as a place where spatial context is embodied (Longhurst, 1997; Moss & Dyck, 2003). Drawing on conceptualizations of intersectionality, health geographers have begun to explore how health (and ill-health) experiences are informed by identities, and concurrently shaped in place by broader societal context (Valentine, 2007). While this work lays a solid foundation for current investigations of health, environment, and gender, the studies described herein build on these theoretical pillars to introduce the concept of social epigenetics, using SLE as a case study.

2.2 Research design

This research employs a pragmatic multimethods design framed by ecosocial theory and biopsychosocial theory, complemented by a feminist approach that centres gender and intersecting identities. The specific methods used include scoping review and qualitative research techniques, such as focus groups and interviews. An integrated knowledge translation approach was employed throughout the research process to engage knowledge users and facilitate bi-directional knowledge sharing.

2.2.1 Multimethods design

Multimethods research designs can be broadly defined as the use of two or more methods within a particular study or research agenda (Hunter & Brewer, 2016). Multimethods designs are employed when "two or more research projects are conducted, each complete in itself, to address [the] research questions" (Morse, 2003). In contrast to mixed methods study designs, which generally combine quantitative and qualitative approaches to answer a particular research question, multimethods designs allow for greater freedom of methodological choices (Hunter & Brewer, 2016). Multimethods also allows the researcher to approach research questions from multiple perspectives or paradigms, thereby constructing a more dimensional view of the research problem and potential solutions, and minimizing researcher bias (Cresswell, 2015). Overall, multimethods recognizes that each individual method has strengths and limitations, and allow the researcher freedom to choose what is most appropriate for the information sought. Multimethods research designs are increasingly used in research investigating biological-social issues, as these types of research questions necessarily draw from two or more paradigms (e.g. biological and social sciences), each with their own sets of methods and assumptions (Hunter &

Brewer, 2016). Multimethods studies have also been shown to be effective modalities for feminist praxis, and in particular for examining the intersectional nature of gender and other identities in health and social issues (Hesse-Biber & Griffin, 2016).

In designing this research, we heeded Elliott's (1999) guidance that "the question shall determine the method". A multimethods design was therefore appropriate as each method supports a specific question and objective within the broader research goal (Morse, 2003). This design, and methodological plurality, also allows for the exploration of SLE at different scales (e.g. population level vs individual level). A concurrent design was utilized in which data were collected and analyzed in parallel, and findings informed the broader research agenda.

2.2.2 Theoretical framing

In line with the use of a multimethods design, this research draws epistemologically on pragmatism. Pragmatism is a philosophic tradition that highlights the existence of multiple observable truths. In this line of thought, human actions, beliefs and experiences are inextricably linked with, and shaped by, situational context and environments (Kaushik & Walsh, 2019). With respect to methodology, pragmatic practice emphasizes the importance of choosing research tools that best fit the needs and constraints of the research question and context of knowledge use (Ramanadhan et al., 2021).

The health issues discussed herein are further framed by ecosocial theory, biopsychosocial theory, and feminist perspectives. Ecosocial theory was first proposed by Krieger (1994; 2011b) to describe the multiple and entangled factors of who and what drive health inequities. In this framework, all levels of biological, ecological, and social organization are considered in relation to health, from cells to organs to individuals, and families to

communities and societies (Figure 1) (Krieger, 2012). Ecosocial theory draws on lifecourse theory and history, political economy and ecology, and societal power to situate the development of health and disease within a broader context. We employ this lens, and particularly Krieger's conceptualization of embodiment, to explore the biological-social interplay in SLE at a variety of scales, and as assembled in place.

This research is similarly informed by biopsychosocial theory to understand the convergence between biological (e.g. physiological), psychological (e.g. thoughts, emotions, behaviours), and social (e.g. socioeconomic, socioenvironmental, cultural) systems in (re)producing health and illness (Miles, 2013). In contrast to the traditional "biomedical" models developed and employed in Western contexts, biopsychosocial theory takes a wider approach that considers not only biological factors, but also psychological and social factors, in deconstructing patterns of disease. Biopsychosocial models have commonly been implemented in the study of mental illness and disorders (Bolton & Gillett, 2019), and have more recently been proposed as appropriate models for the holistic study of SLE (Kinsey et al., 2018).

While ecosocial and biopsychosocial theories both highlight the importance of social experiences in constructing health and illness, scholars have noted some shortcomings in their conceptualizations of gender and intersectionality (Merz et al., 2023). Given the significant social disparities seen in SLE populations, this research takes a feminist approach that centres gender and intersecting identities throughout the research process (Valentine, 2007). Feminist theory is therefore integrated into all stages of the research process, from the generation of research questions to the development of methodologies and particularly, in analysis of the findings (Hesse-Biber & Griffin, 2016). In adopting feminist perspectives, this work recognizes

the complexity of bodies, the importance of lived experience, the reflexive nature of research, and that knowledges are situated (Dyck, 2003; Haraway, 1988).

2.2.3 Integrated knowledge translation (iKT)

Knowledge translation (KT) is defined by the Canadian Institutes of Health Research as "a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically-sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the health care system" (CIHR, 2015). Integrated knowledge translation (iKT) is a type of KT wherein knowledge users, or individuals who are likely to use the knowledge generated through research (e.g. in individual or group decision-making), are included throughout the research process (CIHR, 2015). From the conception of research questions through to the interpretation of results, iKT incorporates regular touch points with knowledge users to provide input, feedback and assist in contextualizing research findings. Studies using iKT have been shown to better meet knowledge user needs, and produce knowledge that is more rapidly taken up in policy and practice, by co-producing (i.e. researchers together with knowledge users) knowledge that is more useful, useable and meaningful (Graham et al., 2018; Jull, Giles, & Graham, 2017; Nguyen et al., 2020).

An iKT approach was embedded in the research design for two purposes: i) to engender the contributions of knowledge users to the research process, and ii) to facilitate the mobilization of research findings. With these goals in mind, a diverse research team was assembled including three researchers, one SLE clinician/researcher, and one patient partner. The team represented both trainees (i.e. a PhD student), staff (i.e. a research assistant) and senior researchers (i.e. faculty) spanning geography, medicine, and bioinformatics. The research team met virtually

every two weeks throughout the research process to discuss ongoing activities. All members of the research team were kept appraised of research processes and had the opportunity to provide input and feedback at all stages.

2.3 Research techniques

In line with our multimethods approach, several research techniques were employed to explore different facets of SLE. Each research technique was selected based on its suitability to address the research questions and objectives set out, taking into account the practical constraints of conducting research (e.g. time, funding, feasibility) (Ramanadhan et al., 2021). The four main techniques employed were narrative review, scoping review, focus groups and interviews.

2.3.1 Narrative review

Narrative reviews are a common technique used in health research to summarize the relevant literature on a particular topic. Narrative reviews are not explicitly systematic, but rather endeavour to explore and synthesize (e.g. "narrate") concepts, debates, or issues in the given field, as well as to identify potential knowledge gaps (Baethge, Goldbeck-Wood, & Mertens, 2019).

To meet research objective #1, a narrative review of the relevant disciplinary literature was undertaken related to health geography and social epigenetics. Studies were selected based on their relevance to temporal disciplinary shifts in health geography as well as the parallel literature in genetics, social epidemiology and population health.

2.3.2 Scoping review

Scoping reviews are a type of systematic literature review that aim to collect and synthesize the existing evidence on a particular topic. The goal of a scoping review is to identify, broadly, what is known (e.g. main concepts, theories and sources) as well as any knowledge gaps (Tricco et al., 2018). In line with systematic reviews, scoping reviews take a methodical approach to reviewing the literature, wherein specific steps are taken throughout the research process and reported transparently. However, while systematic reviews seek sources of evidence that answer a specific research question, the purpose of a scoping review is to identify the coverage – or "scope" – of literature on a topic more generally (Munn et al., 2018). A scoping review is therefore an appropriate tool when the breadth of evidence is unknown, or the evidence for the research topic is still emerging (Munn et al., 2018).

To meet research objective #2, a scoping review was undertaken to investigate and synthesize existing literature on the social factors influencing the development of cardiovascular disease (CVD) in SLE. A scoping review was employed as the topic was broad, and the extent of knowledge pertaining to the topic was unclear, even after preliminary searching. In addition to seeking research findings on the topic, we were equally interested in determining the knowledge gaps to inform future research studies. To our knowledge, this was the first knowledge synthesis conducted on this topic. The specific data collection and analysis methods employed are described in detail below (see Sections 2.4.1 and 2.5.1).

2.3.3 Focus groups

Focus groups are a qualitative research technique commonly employed across health and social research. Focus groups can be defined as an organized group discussion used to explore a

particular issue, topic, or experience (Kitzinger, 2005). Typically, a focus group will be facilitated by one or more researchers with pre-determined questions or topics for discussion. The "focus" aspect therefore involves some sort of shared or collective activity, while the "group" size can range depending on the research needs (Kitzinger, 2005). Focus groups are useful for exploring participants' own thoughts, ideas, perceptions and concerns related to the topic at hand in the participants' own voices (Lehoux, Poland, & Daudelin, 2006). In contrast to other qualitative data collection techniques (e.g. interviews), focus groups provide a unique opportunity for participants to interact and build on one another's comments within the context of social interaction (Hay & Cope, 2021). A focus group environment may therefore assist in building rapport among participants with similar experiences, leading participants to share more openly (Hay & Cope, 2021). In addition to facilitating the collection of data, research indicates that focus groups may also function to empower participants by disseminating knowledge, building community, and encouraging input in the research process (Hall et al, 2022).

In line with research objective #3, a webinar-style focus group was employed in which key informants were invited to reflect and provide feedback on two research deliverables: a patient education document describing the risks of CVD in SLE, and an online calculator tool specifically designed for patients with SLE that can be used in CVD risk monitoring. Key informants were selected based on their roles in the SLE community (e.g. representatives from advocacy organizations), SLE research (e.g. researchers and rheumatologists), or expertise in cardiovascular disease (e.g. representatives from advocacy organizations and cardiologists). The meeting was held virtually to facilitate attendance from key informants across the country as well as the research team, who are based in both Ontario and Alberta. As this meeting happened in June 2022 during the COVID-19 pandemic, a virtual meeting was also necessary to protect the

health and safety of all participants, many of whom are/were chronically ill or otherwise immunocompromised. The specific data collection and analysis methods employed are described in detail below (see Sections 2.4.2 and 2.5.2).

2.3.4 Interviews

Interviews are another qualitative research practice widely implemented in health research, but in contrast to focus groups, position the researcher and participant in a one-on-one setting. Interviews similarly explore exploring participants' thoughts, ideas, perceptions and concerns on a particularly topic, but due to the on-on-one nature of the session, often allow the researcher to collect and probe for more rich, in-depth data (Coleman, 2019). While there are a range of interview approaches (e.g. unstructured vs structured), these interviews were semi-structured, which means the researcher uses a pre-determined list of questions and probes (i.e. interview guide), but still has some flexibility for the participant to guide the discussion, or to explore particular ideas or experiences more in-depth (Brinkman, 2020). The practice of combining focus groups with interviews has been shown to enhance data richness by exploring the topic at both the individual and social/contextual levels, and also allows researchers to triangulate qualitative findings to determine their validity (Lambert & Loiselle, 2008).

To complement the focus group, semi-structured in-depth interviews were conducted with patients with SLE. These interviews similarly engaged those living with SLE to reflect and provide feedback on the patient education document and online calculator. Patients were recruited from MC's rheumatology practice in Calgary, Alberta. Interviews were conducted virtually for logistical reasons (e.g. scheduling, minimizing travel) and similarly for health and

safety practices during the COVID-19 pandemic. The specific data collection and analysis methods employed are described in detail below (see Sections 2.4.2 and 2.5.2).

2.4 Data collection

2.4.1 Scoping review

The data collection process for this scoping review was guided by Arksey & O'Malley's (2005) methodological framework for conducting scoping reviews in conjunction with the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines (Tricco et al., 2018) to ensure transparency and rigour.

2.4.1.1 Search strategy

In line with research objective #2, a search strategy was designed to encompass three main concepts: SLE, CVD and social factors. Herein, we define social factors as circumstances that impact a person's health or wellbeing that are rooted in social systems, environments, interactions or experiences. Development of the search strategy was done in conjunction with Jackie Stapleton, a University of Waterloo librarian with extensive experience in conducting and publishing systematic and scoping reviews. For each main concept, a list of relevant search term was established (Figure 2). The search terms for CVD were developed in collaboration with MC, a rheumatologist specializing in SLE. The search terms for social factors were developed based on the social determinants of health framework (Wilkinson & Marmot, 2003), supplemented by key references in the biopsychosocial literature (Kolk, 2015; Maté, 2003) and biospsychosocial studies focusing on SLE (Kinsey et al., 2018) or CVD (Daniel, Moore, & Kestens, 2008). The

search strategy was iteratively reviewed by the research team, and all members provided input and feedback on the search terms. The final search string is detailed in Figure 3.

Four databases were chosen for conducting the searches based on their relevance to the biopsychosocial literature (e.g. subject matter is biology, psychology, health or social sciences): PubMed, Scopus, PsychINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The four databases were searched for articles published between 2000-2022 to correspond with initial publication of the determinants of health framework (Wilkinson & Marmot, 1998) and the time of conducting the searches. Articles were searched in English only due to the language proficiency limitations of the team. The search was limited to peer-reviewed journal articles only. Test searches were performed in conjunction with the librarian to identify and adjust or remove search terms generating non-specific results. A sample search strategy is detailed in Figure 1. Searches were conducted in July 2022. Studies identified by the search strategy were imported into Covidence software (www.covidence.org) and duplicate records removed.

2.4.1.2 Study selection

To determine whether the collected articles fulfilled the criteria for the scoping review, a two-phase screening process was employed: 1) title and abstract screening, and 2) full-text screening. Title and abstract screening were conducted in duplicate with a research assistant using pre-determined selection criteria. Included studies were required to address all three of: SLE, CVD, and social factors and utilize an adult (>18 years) study population. Pediatric studies were excluded due to differences from adult SLE in etiology, experiences and health trajectories (Knight et al., 2016; Mina & Brunner, 2010; Tarr et al., 2014). Animal studies were excluded

due to a lack of transferability with respect to social dimensions. Clinical case studies and reviews were also excluded, although the references of relevant reviews were screened for any additional studies not obtained from the initial search.

Screening was performed independently using Covidence and any conflicts were resolved by discussion with the research team. Full-text screening was conducted in duplicate with at least one other researcher from the team, with each researcher screening a minimum of two studies. Our patient partner participated in the process as a third screener with support from the first author in reviewing the studies. A decision was made to modify the selection criteria during full-text screening to focus on "first order" social determinants (i.e. a social aspect of being), rather than "second order" determinants (i.e. a behaviour or state driven by social aspects of being). Thus, some previously included concepts (see Figure 3) were excluded from the final analysis. This process is represented in the PRISMA chart shown in (Figure 4).

2.4.2 Focus group

A focus group-style webinar was held online via Zoom with key informants. The purpose of this meeting was to obtain knowledge user input, feedback and recommendations on the lay document and future SLE-CALCULATOR tool, as well as to qualitatively explore knowledge, attitudes and practices related to CVD in SLE more generally. This protocol was approved by the University of Waterloo Office of Research Ethics (ORE #44339).

2.4.2.1 Recruitment

N=5 key informants participated in the focus groups. Key informants were purposively sampled based on their expertise in either SLE or CVD. We specifically targeted national and

provincial-level SLE-related advocacy organizations, other health-related organizations closely related to SLE (e.g. Arthritis Society), CVD-related advocacy organizations, SLE rheumatologists/physicians, and researchers with established experience in SLE. A balance was sought between types of key informants to achieve maximum variation in the dataset. After initial contact with identified key informants, snowball sampling was implemented, which is a recruitment technique in which existing participants can identify and/or invite additional participants from their own networks (Hay & Cope, 2021). In this case, key informants were encouraged to invite additional members of their organizations.

Selected key informants were contacted by email and provided with a letter of information and details for the event. When participants responded with interest, they were provided with consent materials and a copy of the lay document to review before the meeting.

2.4.2.1 Webinar

Ahead of the meeting, a semi-structured facilitator guide was developed with open-ended questions and probes to stimulate discussion around four main themes: i) experiences of SLE, ii) knowledge and experiences about CVD in SLE, iii) the lay document and iv) the SLE-CALCULATOR. A minute-by-minute agenda was also prepared to ensure all topics had adequate time for discussion. The facilitator guide and agenda were reviewed in full by the research team, including our patient partner, and all team members provided input and feedback. The facilitator guide was piloted ahead of the meeting to ensure all questions were understandable and solicited discussion around anticipated topics.

The focus group was 90 minutes in length and was held via Zoom videoconferencing. The meeting was audio and video recorded. The meeting was structured with a 30-minute

webinar followed by 60 minutes of discussion. The webinar portion provided an overview of the research team, the purpose and objectives of the research, and the research deliverables to be discussed (i.e. lay document and SLE-CALCULATOR). The discussion portion was facilitated according to the facilitator guide (Appendix 1) and agenda. During discussion about the lay document, the lay document was able to be viewed by all participants using the screen share feature. The facilitator managed the discussion to ensure equal participation and that all voices were heard. All research team members attended the session to observe and add to the discussion where necessary. After the webinar portion and following the discussion, all participants had the opportunity to ask any questions or provide any additional information or comments.

After the webinar, participants were sent a thank you letter via email to thank them for their time and ideas. Participants were also asked if they would like to receive future project updates, and/or invitations to participate in future research activities. The webinar transcript was transcribed verbatim for qualitative analysis.

2.4.3 Interviews

One-one-one, semi-structured in-depth interviews were held online via Zoom with patients with SLE. The purpose of these interviews was to obtain knowledge user input, feedback and recommendations on the lay document and future SLE-CALCULATOR tool, as well as to qualitatively explore knowledge, attitudes and practices related to CVD in SLE more generally. This protocol was approved by the University of Waterloo Office of Research Ethics (ORE #44339).

2.4.3.1 Recruitment

Interviews were conducted with N=5 patients with SLE. Participants were adults over the age of 18 years who had previously received a diagnosis of SLE, and were receiving current treatment or follow-up care from Dr. May Choi's clinical rheumatology practice in Calgary, Alberta, Canada. Participants were purposively sampled from Dr. Choi's clinic. Participants who had previously agreed to be contacted for research purposes were phoned by clinic reception to determine whether they would be interested in the current project. If participants agreed, they were phoned directly by Dr. Choi to confirm their contact information and obtain permission to share this information with researcher conducting interviews. If participants agreed, they were contacted by the researcher via email with a description of the project, letter of information and consent materials. Participants were followed up with twice by email, and twice by phone call. If no response was received, participants were considered not interested and removed from the list of prospective participants. If participants responded with interest, a 60-minute virtual interview was scheduled at a time of their convenience.

2.4.3.1 In-depth Interviews

Ahead of the meeting, a semi-structured interview guide was developed with open-ended questions and probes to stimulate discussion around four main themes: i) experiences of SLE, ii) knowledge and experiences about CVD in SLE, iii) the lay document and iv) the SLE-CALCULATOR. The interview guide and agenda were reviewed in full by the research team, including our patient partner, and all team members provided input and feedback. The interview guide (Appendix 1) was piloted ahead of the meeting to ensure all questions were understandable and solicited discussion around anticipated topics.

Interviews ranged from 28-53 minutes in length, and were conducted online via Zoom videoconferencing. All interviews were audio and video recorded. The structure of the interviews was modelled based on the structure of the previously conducted webinar (described above), but compacted, with 15 minutes allotted for presentation and 45 minutes for discussion. All material presented and discussion procedures were the same, but the interviews were conducted one-on-one with only one researcher and one participant.

After the webinar, participants were sent a thank you letter via email to thank them for their time and ideas. Participants were also asked if they would like to receive future project updates, and/or invitations to participate in future research activities. All interviews were transcribed verbatim for qualitative analysis.

2.5 Data analysis

2.5.1 Data charting & Analysis

The data were charted using an extraction template from Covidence that was amended to fit the specific needs of this study. The data was charted independently and reviewed for content and completeness by the research team. The following variables were sought during the charting process: country/region in which the study was conducted, theory/framework used, purpose/aim, study design, start/end dates, social variable(s) studied, operational definition(s) of social variable(s) studied, cardiovascular outcomes measured, population description, participant base/affiliation (e.g. universities, hospitals, other), participant inclusion/exclusion criteria, total number of participants, key findings, study limitations, study strengths, knowledge translation (KT) plan, and co-production of knowledge (i.e. whether knowledge users were included in the

research process). Critical appraisal of individual sources of evidence was not performed (Munn et al., 2018) as this was a scoping review.

The included studies were grouped and analyzed thematically by the social factors studied to synthesize existing knowledge and determine knowledge gaps.

2.5.2 Qualitative Analysis

Qualitative data from interviews (N=5) and the focus group (N=1) were analyzed thematically using NVIVO 14 software. Two code books were developed, one for the interviews and one for the focus group (Appendix 2). Unique codes were assigned to overarching themes and sub-themes to collect relevant sections of text corresponding to each theme, and to determine their relative frequencies within the transcripts. Codes were developed deductively (e.g. codes determined based on prior literature searching and possible responses to questions) and inductively (e.g. emerged from the data during analysis) (Hay & Cope, 2021). Deductive codes were developed related to SLE impacts, knowledge about SLE and CVD, broad categories of recommendations for the lay document, and general preferences for the SLE-calculator tool. Inductive codes were developed as transcripts were continuously read and reviewed throughout the analysis process. When themes emerged that were not in the codebook, they were added, and data was iteratively reviewed for relevant text. Inductive codes were developed related to CVD experiences, identities, lifestyle behaviours, and specific recommendations for the resources. Using a combination of deductive and inductive codes guided the analysis to seek specific information that could be actioned to shape the resources, while creating space for emerging themes and privileging participant voices. Coded sections of text were reviewed within the

context of each code to ensure consistent interpretation of the text across transcripts and throughout the analysis process.

2.6 Methodological rigour

Rigour in the research process is critical for ensuring the validity, reliability, dependability and credibility of research findings (Anderson, 2010). As stated by Johnson et al. (2020), "rigour in the research process and results are achieved when each element of study methodology is systematic and transparent through complete, methodical, and accurate reporting". To this end, a number of considerations to address rigour were employed within each of the individual methods included within the broader research design.

2.6.1 Rigour in scoping reviews

To address persisting issues and gaps in rigour and reporting of scoping reviews, the PRISMA-ScR guidelines and checklist were introduced in 2018 (Tricco et al., 2018). To ensure rigour in the scoping review herein, the PRISMA-ScR guidelines were consulted and all requirements for reporting were met. To further guide the scoping review process, we followed Arkey and O'Malley's (2005) methodological framework. This framework outlines five steps for conducting scoping reviews and identifies best practices for each stage of: 1) identifying the research question, 2) identifying relevant studies, 3) study selection, 4) charting the data, and 5) collating, summarizing and reporting the results. Covidence software was used for all stages of analysis. To assist in the accurate interpretation of results, the acquired evidence was iteratively discussed among the research team, including two SLE clinician-scientists (MC and KC) and a patient partner (CS).

2.6.2 Rigour in qualitative research

To establish rigour in the qualitative stages of the research design, a number of strategies were employed throughout the research process. During recruitment, purposive sampling was used to intentionally seek out research participants rich in contextual knowledge and experiences in order to optimize the data collected. To do this, key informants were recruited who would have strong connections with the SLE community (e.g. representatives of advocacy organizations) or experience with patient education (e.g. other health-related organizations and clinicians). Moreover, we sought out maximum variation within the participant groups (e.g. education/training, experience, identities) to integrate multiple perspectives and construct a more holistic and representative view of SLE. Considering maximum variation and collecting contradictory evidence are two established ways to reduce research bias in qualitative data collection processes (Stratford & Bradshaw, 2021).

During the data collection process, member checking was employed throughout interviews and the focus group. This technique entails summarizing and reiterating the content provided by participants when discussing interview questions and asking them to confirm the researcher's interpretation, thereby minimizing miscommunications and ensuring accurate representation of results (Candela, 2019). Efforts were made to build rapport and trust with participants at all stages of contact, through scheduling through to interview follow up, in order to ensure participants were comfortable and reduce any perceived power imbalances. Throughout the data collection process, peer review and peer debriefing were utilized regularly by discussing emerging results and interpretation with the research team, including an SLE physician and patient partner. Interviews were conducted to a point of saturation, at which no new themes were emerging (Stratford & Bradshaw, 2021). All interviews and the focus group were audio and

video recorded, and the transcripts were proofread. Researcher notes were taken during the recruitment process as well as during and immediately after interviews and the focus groups to document and reflect on interactions with participants.

Qualitative data sources were triangulated during analysis and interpretation to confirm validity and construct "a more complete picture" of the research findings (Farmer et al., 2006). Specifically, methodological triangulation was done through the use of different qualitative methods (e.g. focus groups and interviews), data triangulation was achieved through the use of multiple participant groups (e.g. key informants and patients with SLE), and investigator triangulation was found through collaboration with the research team (Carter et al., 2014).

2.7 Knowledge translation

2.7.1 SLE-CALCULATOR tool

The SLE-CALCULATOR (Systemic Lupus Erythematosus CArdiovascuLar Disease Event Risk PrediCtion Using Machine LeArning Techniques and NOvel ThRombotic Autoantibodies) is a tool under development for predicting risk of CVD in individuals with SLE. Currently, no CVD risk prediction tools exist specific to SLE, and risk prediction tools for the general population perform poorly in this context. In contrast to risk prediction tools for the general population, the SLE-CALCULATOR uses machine learning techniques to incorporate traditional CVD risk factors, SLE-specific variables, and novel autoantibodies into a single algorithm. This tool is currently being developed by collaborators at the University of Calgary, Massachusetts Institute of Technology (MIT) and Harvard University, and when validated, will be publicly available online, free of charge, for use by individuals with SLE, their physicians, and/or other healthcare professionals.

While a detailed methodology describing the SLE-CALCULATOR development process is outside the scope of this dissertation and will be detailed elsewhere, the studies herein contribute to the knowledge translation aims of this project by engaging knowledge users to assist in co-producing the vision for this future tool.

2.7.2 Patient education resource

In order to support the SLE-CALCULATOR and knowledge translation aims of this project, a lay language patient education resource was collaboratively developed by the research team. The purpose of this document is to accompany the SLE-CALCULATOR tool, as well as to be disseminated separately to increase knowledge and understanding of CVD among the SLE community.

Based on the existing literature, and anticipated knowledge user needs, an outline for the resource was developed. The literature surrounding SLE and CVD was reviewed and synthesized, and key messages were prioritized for inclusion in the document. Professional graphic design services were contracted to design the document and graphics. The research team reviewed the initial draft and provided feedback. Team recommendations were used to revise the resource prior to the study described in Manuscript #3. A copy of the resource reviewed in this study is included in Appendix F.

Topics covered in the document include what is CVD, why those with SLE are at higher risk, who within the population is most at risk and prevention/management strategies to reduce risk. The document is written in plain language for a general audience (i.e. eighth grade reading level (Hutchinson, Baird, & Garg, 2016) and includes links to additional evidence-based resources for more information.

2.7.3 Dissemination of research findings

To mobilize the findings from this research, a knowledge translation (KT) plan was developed and implemented. While the integrated knowledge translation approach incorporated throughout the research process facilitates knowledge mobilization to key stakeholders involved in the project, who also provide input and feedback on the research, the KT plan focuses on dissemination more broadly to both knowledge users and the general public.

The research findings in Manuscript #1 are largely theoretical and methodological in nature and therefore primarily serve the needs of academics. As a result, these findings were published in the peer-reviewed literature and presented at academic conferences including the 19th International Medical Geography Symposium and the Canadian Association of Geographers annual meeting.

The knowledge synthesis in Manuscript #2 pertain additionally to clinicians and healthcare practitioners, advocacy groups, those interested in health prevention and patient education, as well as patients themselves. In addition to submission to the peer-reviewed literature and academic conferences, these findings will be shared through a community outreach event for the SLE community accessible to participants nationwide, and also shared directly with advocacy groups for dissemination through their networks.

The findings from Manuscript #2 identify knowledge gaps in CVD prevention that we aim to reduce through the deliverables (i.e. patient education resource) detailed in Manuscript #3. The findings from Manuscript #2 are therefore used to inform the dissemination plan for Manuscript #3. Manuscript #3 will be submitted to the peer-reviewed literature to serve as a blueprint for fellow academics aiming to co-produce similar resources using iKT and knowledge user perspectives. The patient education resource developed through the process detailed in

Manuscript #3 will be disseminated through several routes: i) publicly available online; ii) as accompanying information for an upcoming SLE-CALCULATOR tool; iii) distribution through partner organization networks (e.g. national and provincial SLE organizations) social media and mailing lists; iv) through rheumatology clinics; v) through rheumatology mailing lists; and vi) through SLE patient mailing lists, as well as vii) through a community outreach event for the SLE community.

CHAPTER THREE

Manuscript #1: From social determinants to social epigenetics: health geographies of chronic disease

E. Shantz & S.J. Elliott. Published in Health & Place.

Abstract

Social epigenetics explores relationships between social factors and health inequities embodied at the molecular level. Through modulating gene expression, epigenetic changes resulting from human-environment interactions may play a role in shaping health trajectories. This paper applies a health geography lens to explore the potential and support for conducting social epigenetic studies of chronic diseases with complex and dynamic etiologies. In so doing, we argue that social epigenetics presents a novel space for investigations of health and disease that is transdisciplinary and builds upon new understandings of bodies and place-based experiences. Given gender disparities in chronic diseases, we adopt a feminist perspective that cogitates the transactive relationships between gender and health/ill-health as mediated by biosocial processes at a variety of scales. Looking forward to the practical undertaking of social epigenetic studies, we assess existing theoretical and methodological support as well as insights to be gained. Reflecting upon the central tenets of health geography, we propose a unique positionality for health geographers to drive this field forward.

Keywords: health geography; epigenetics; social epigenetics; chronic disease; gender.

1. Introduction

The advent of molecular biotechnologies raises questions about the role of cellular processes in mediating health and disease. For many years, researchers delved into the human genome, hypothesizing whether each individual's unique assortment of genes dictated their health trajectories. More recently, the discovery of epigenetics has shifted the molecular paradigm, as it has become apparent that our genes are indeed not static or fixed; rather, epigenetic modifications permit our genes to become malleable, plastic entities with the power to respond to environmental stimuli and adapt our bodily processes according to place-based contexts (Cavalli & Heard, 2019).

Concomitantly, over the past couple of decades, health geographers have explored the role of experiences of place in shaping health; indeed, as a sub-discipline, we often referred to the process of 'place getting under the skin' of individuals thus manifesting in states of ill health (Gatrell & Elliott, 2014; Gesler & Kearns, 2005). We now see this same analogy in papers written by epigeneticists (Shields, 2017). That is, as researchers continue to uncover epigenetic patterns informing health and disease, the field has taken an unprecedented turn into what has traditionally been the territory of social science inquiry. By considering the multiple and measurable epigenetic effects observed in relation to physical and chemical environmental factors, it has recently been proposed that similar molecular changes might be observable as a direct result of interactions with society and social systems. Termed "social epigenetics", this rapidly emerging line of investigation seeks to determine whether specific epigenetic patterns can be found among populations grouped by various social factors. In particular, a burgeoning body of work has begun to explore the potential roots of embodied health inequalities in adverse

social circumstances such as poverty, trauma (Mulligan, 2016), and toxic environmental exposures (Feil & Fraga, 2012).

Epigenetics has revolutionized thinking in biologically-linked conceptualizations of human-environment interactions in the context of disease. In this paper, we explore the potential for social epigenetics studies of chronic disease through the lens of health geography. In so doing, we argue that social epigenetics represents a distinct and unique transdisciplinary space for investigations of health and disease that build upon new understandings of bodies and place-based experiences. Given disparities in prevalence and experiences of many chronic diseases, we concomitantly reflect on the roles that gender and environment play in producing and re-producing health and ill-health, advocating for the necessary integration of sex and gender-based analyses in social epigenetic studies. In exploring the theoretical and methodological support for the social epigenetic paradigm, and the innovations necessary to drive this line of inquiry forward, we position health geographers at the nexus of this paradigm shift.

1.1 Chronic disease

Chronic diseases represent a significant global health burden (World Health Organization, 2019). They are characterized by a sustained period of illness accompanied by an associated physical impairment or disability (Bernell & Howard, 2016). Chronic diseases are generally not caused by infection (i.e. bacteria or virus), and therefore are not transmissible (Shantz & Elliott, 2020). They generally cannot be prevented by vaccines, do not resolve spontaneously, and although they can be treated, cannot be cured. The four main classes of chronic diseases responsible for the majority of related deaths are: cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes (World Health Organization, 2019). However,

a number of other conditions also fall under this definition – notably allergic and autoimmune diseases – which represent a rising global burden of morbidity and mortality (Shantz & Elliott, 2020).

In contrast to infectious diseases, which can be traced back to a single origin, chronic diseases are complex and multifactorial in origin (Vineis, 2018). They may arise as the result of a combination of health-damaging and lifestyle behaviours, as well as exposure to poor socioenvironmental conditions over time (Shantz & Elliott, 2020). Although many of these factors are external in nature, an individual's intrinsic biological composition also plays a role, as some may be predisposed to developing chronic conditions (i.e. genetics). In recent decades, researchers have attempted to unravel the complex causalities of chronic disease in an effort to target preventative measures and interventions. Yet, while many factors have been identified (e.g., obesity, nutrition, lack of physical activity, smoking, alcohol, etc.), the specific etiologies of most chronic diseases remain unclear (Cockerham, Hamby, & Oates, 2017).

1.2 Epigenetics & Social Epigenetics

Molecular and genetic technologies have allowed us to unearth many complexities of the human genome and its role(s) in mediating health and disease. Comprised of deoxyribonucleic acid (DNA) strands organized into chromosomes, our genes are inherited from our respective biological parents and serve as the "blueprint" for all cellular processes. At a broader scale, the temporal and relational expression of different genes translates into the homeostatic functioning of bodily systems. Due to the processes through which genes are inherited, and the fundamental requirement of the genetic code for life-sustaining processes, an individual's particular array of genes (i.e. genome) cannot be changed. However, in order to respond and adapt to different

environments, organisms – humans, animals, plants, etc. – have developed unique mechanisms to control the operations of their genes. These mechanisms are collectively termed epigenetics (Feil & Fraga, 2012).

The field of epigenetics has characterized a series of molecular processes by which our environment alters gene expression at the cellular level. Following an environmental stimulus, epigenetic mechanisms function to effectively silence or activate selected genes within the genome. These silencing and activation mechanisms may act directly on genes themselves by the addition of chemical signals (i.e. methylation, acetylation), or by directing the repackaging of the DNA strand on which the gene is located to make it more or less accessible for "reading" (Chung et al., 2016). The process of reading and producing the respective proteins encoded by genes is referred to as "gene expression". Through silencing (i.e. decreasing) or activating (i.e. increasing) gene expression, in addition to other epigenetic mechanisms directing protein production, new functional patterns emerge within and between cells. As we scale up to the organism level, these changes manifest as bodies' abilities to dynamically respond and adapt to environmental context, both transiently and over time (McEwen, 2012).

The term "social epigenetics" has emerged to describe how the social environment, specifically, might influence bodies at the molecular scale through mediating gene expression (E. Chung et al., 2016; Cunliffe, 2016). Recognizing the potential for epigenetic changes to translate into longer-term health trajectories or health outcomes, social epigenetics has been proposed as a potential mechanism driving health disparities. Researchers posit that epigenetic changes occurring at particular stages of development – termed critical or sensitive periods – may have long-term impacts on health, particularly with respect to complex chronic diseases (McDade et al., 2017; Shields, 2017). It is thought that social factors "get under the skin" through the stress

response, which exerts a range of impacts across bodily systems including immunity, neural pathways, and endocrine secretion (McEwen, 2012). Repeated or chronic stress has the potential to fundamentally change the functionality of these systems at the molecular level through epigenetic changes, as the body is forced to adapt over time. In the social environment, stress may be triggered through individual interactions and experiences, or at a broader level through structural factors, such as systemic racism, gender discrimination, poverty, and marginalization (Notterman & Mitchell, 2015).

2. The Social Environment & Health

In order to explicate the novelty of social epigenetics, we set a foundation with the classic works concerned with relationships between the social environment and health (Evans, Barer, & Marmor, 1994; Moore & Carpiano, 2020; Wilkinson & Marmot, 2003); in particular, we focus primarily on the literature from the areas of the social determinants of health and biosocial investigations.

2.1 Social determinants of health

The social determinants of health emphasize the various nonclinical factors, including social, economic, political, cultural, and environmental factors, influencing health (Notterman & Mitchell, 2015). This perspective prioritizes the places and conditions into which people are born, grow, work, live, and play in shaping health and ill-health (World Health Organization, 2018). These conditions of daily life are, in turn, necessarily shaped by broader structural forces including social policies and systems, economic policies and systems, and overarching political systems (World Health Organization, 2018). The social determinants of health framework

therefore implies an iterative relationship between individuals and their environments in which the environment influences behaviour, and behaviour influences health; therefore, changes to the environment can lead to different health behaviours and subsequent health outcomes (Wilkinson & Marmot, 2003).

A large body of empirical work supports the relationships between the social determinants and population health. Across a plethora of studies conducted in a variety of contexts (e.g. geographic locations, populations), the consensus remains – experiencing adverse social circumstances results in poorer health and increased risk of disease (Evans et al., 1994; Frank et al., 2015). (It is important to note that these effects have been shown to be modifiable by the introduction of equity-building policies at a variety of levels (e.g. structural and public sector policies; social and community support; health education and lifestyle interventions) (Dahlgren & Whitehead, 1991; Whitehead, 1992; Frank et al., 2015).

Given these connections, it is apparent that somehow the social environment "gets under the skin" (McEwen, 2012; Shields, 2017). Further, it is reasonable to hypothesize that, indeed, health inequities rooted in the social determinants of health could be revealed at the epigenetic level. However, even as we continue to cache evidence supporting the notion that social factors significantly impact health and disease trajectories, policy implications of such knowledge remain consistent – advocating for racial and gender equality, improved social policies, alleviation of poverty, and global re-distributions of wealth and resources (Bambra et al., 2010). In this respect, while social epigenetic research stands to add interesting insights to our understandings of socio-environmental impacts on health, it does not substantially reform the ultimate goals of the prevailing line of inquiry. Nonetheless, there is tremendous potential for social epigenetics to reveal itself as a ligature binding social circumstances to biology in a way

that impacts both current state(s) of health and future health trajectories; a link which, despite such evidence for the social determinants of health, has largely been overlooked.

2.2 Biosocial studies

One area of health research which has devoted a great degree of consideration to the mechanisms mediating the biological-social link in chronic disease is the burgeoning area of biosocial studies. Herein, "biosocial" refers to the dynamic ways in which biological identity is shaped by the surrounding social context (Wiese et al., 2018). Indeed, many chronic diseases have been conceptualized as biosocial, with their development, experiences, and outcomes being "more than biological and more than social" (Kinsey et al., 2018, pg. 183). This resulting body of work largely revolves around the concepts of stress and allostatic load. When an individual faces repeated instances of stress, either physical or psychosocial in nature, the associated stress responses coalesce in an accumulated wear and tear on the body (McEwen, 2012). Such chronic stress cycles are produced and sustained by social conditions such as racism, gender discrimination, poverty and other types of marginalization, resulting in poorer health outcomes and embodied health inequalities (Notterman & Mitchell, 2015).

To illustrate, Dowd et al. (2014) investigated how race and socioeconomic status were associated with perceived stress and immune function. Those with lower SES were found to have higher perceived stress and a greater number of stressful life events overall, which were interpreted to be reflected in decreased immune function (Dowd et al., 2014). Prior et al. (2018a) found that more materially-deprived neighbourhoods were associated with higher loads of chronic stress. Perhaps unsurprisingly, this was associated with physical and, to a lesser degree, mental health impacts delineated by a number of stress-related biomarkers. Guided by the similar

geospatial clustering of cardiovascular disease, Daniel et al. (2008) proposed a conceptual framework integrating time and two biosocial pathways through which social disadvantage might promote cardiovascular disease.

Despite growing support for biosocial inquiries of chronic disease, the field is somewhat constrained by its composition. Amidst increasing recognition that the biological and social are inextricably entwined in shaping health and illness, many of these studies represent the work of social scientists attempting to "do biology" or biologists attempting to "do social science". In this respect, we assert that social epigenetics represents a paradigm shift for researchers to engage in truly transdisciplinary work (Elliott, 2011). Here, we refer to 'trandisciplinarity' as an approach to research that goes beyond oft-used 'interdisciplinary' perspectives in health. While interdisciplinary research sees scientists from different disciplines coming together to solve a problem, true *transdisciplinary* research sees a wide variety of scientists engaging alongside a community of knowledge users to inform the entire research process (Elliott, 2011). This approach not only results in more multi-dimensional research questions and investigations, but also functions to bridge the knowledge-to-action gaps critical to solving complex health problems.

2.3 Social epigenetics: What's new?

These transdisciplinary conceptualizations of social epigenetics and their implications for research position the field as necessarily theoretically and methodologically distinct from existing biosocial perspectives. First, social epigenetics marks a significant shift in how we view bodies and biological identities. Previous conceptualizations of biological identity were static, viewing bodies as entities marked by individual abilities and limitations (Wiese et al., 2018).

Armed with an understanding of epigenetics, we move towards a more fluid model of biological identity that views bodies as responsive, permeable, and dynamic (Wiese et al., 2018); in a sense, we now see bodies as having agency of sorts. As such, the underlying mechanisms of social epigenetics both embrace and challenge existing biosocial studies and life course approaches to health in their understandings of chronic disease.

These bodies of work most often view the development of chronic diseases through tabulating an accumulated risk of environmental, lifestyle, and biological factors encountered over time (Ben-Shlomo & Kuh, 2002). Marking a departure from this conceptualization, social epigenetics provides a space to investigate the bidirectionality of relationships between bodies and places, taking into account how these can function in positive and/or negative directions, or may not have discernable impacts on health at all (Rozek et al., 2014). As we cannot disregard the many ways that place-based experiences and social context impact health, we also cannot ignore how health, ill-health and disease, in turn, shape the ways that individuals experience places; this indeed has been a mainstay of the health geography gaze (see, for example: Chouinard, 2018; Crooks, 2007; Crooks & Chouinard, 2006; Gatrell & Elliott, 2014; Twigg & Duncan, 2018). In this respect, social epigenetics belies biosocial pathways that progress in one direction in favour of viewing the environment-body interface as context-dependent, iterative, and dynamic; in essence, the foundation of a health geography perspective.

Second, social epigenetics renders the bodily impacts of socio-spatial context both measurable and quantifiable; for example, by scanning the genome for epigenetic modifications and comparing patterns between individuals or groups (discussed in greater detail below). Rather than measuring transient biomarkers of stress and/or immune activity, epigenetic modifications are more stable, thus providing more reliable data about long-term biological impacts. Epigenetic

markers, in some cases, may even be heritable (Shields, 2017). For example, evidence indicates that children of Holocaust survivors have decreased methylation patterns and increased expression of specific genes compared to control subjects; this effect has been attributed to maternal trauma exposure and subsequent developmental programming in utero (Bierer et al., 2020). To illustrate, early studies indicated that the children of Holocaust survivors experienced higher rates of PTSD and other psychiatric disorders than controls (Yehuda et al., 1998). Social epigenetic studies therefore have the capacity to provide novel insight into the intergenerational consequences of social phenomena. This not only stands to extend our understanding of the production and re-production of health inequities, but also raises ethical questions about collective and individual social responsibility (Meloni & Müller, 2018). In essence, this points to opportunities to expand the epistemologies employed by health geographers who typically major on the lived experience of the health-place relationship (given a lack of methodological tools to do otherwise); binding this with measurable, quantifiable bodily impacts of the socio-spatial context can take us, literally, to the next level of truly transdisciplinary research and hence tremendous potential to influence policies related to equity.

Furthermore, through social epigenetics, we encounter new issues of space and scale. Traditionally within health geography, the individual body has been treated as the ultimate "last stop" for embodiment (Dyck, 2003). However, when we bridge biological pathways into the system, we realize there are multiple scales beneath that of the body, including organ systems, tissue organizations, the cellular/molecular levels and beyond (Nancy Krieger, 2011b). Social epigenetic theorizations aiming to reconcile macro-level social phenomena with their impacts at the molecular scale, therefore, open up these liminal spaces within the body for further exploration.

To be clear, although transdisciplinarity is a central feature characterizing the novelty of social epigenetic investigations, it is not exclusive to this type of research. That is, it is not that other biosocial studies *cannot be* transdisciplinary – ideally, they would be, as different perspectives of health only serve to strengthen research relevance and results. Rather, most biosocial studies performed to date *are not* transdisciplinary. Although they rightfully integrate concepts and investigators spanning various fields of expertise, often these integrations are not inherent in the research questions, and knowledge users are rarely consulted. Although we applaud the steps forward taken by scholars in the field to mend the "silo effects" in health research (Bevc et al., 2015; Shale & Atherton, 2016), we argue that social epigenetics is unique in that it is *necessarily* transdisciplinary. Given the complexity of social and biological systems, as well as the sizeable investments required, a transdisciplinary team is *necessary* to ensure that these studies are i) meaningful, with previous research leveraged appropriately and reasonable interpretations of results; ii) useful in understanding and/or improving some aspect of human health; iii) actively working against marginalization and oppression of vulnerable social groups; and iv) disseminated responsibly to policy makers and the public. We expand on these ideas below, as we illustrate through a discussion of both theoretical and methodological support for social epigenetic investigations of health and place through the example of chronic disease.

3. Theoretical support for social epigenetic studies of chronic disease

Drawing on the literature within health geography and related disciplines, we explore the theoretical support for and explanatory power of social epigenetic approaches.

Health geographers contend with issues of health and disease that are complex in their development, experiences, and outcomes. As such, health geographers must reckon with a

variety of factors interacting within and between scales, and across time. As Nancy Krieger states, "without theory, observation is blind and explanation is impossible" (Krieger, 2011b). In this section, we examine the explanatory power of two theoretical approaches – ecosocial theory and life course studies – through which social epigenetics might be explored. Here, we use examples from the chronic disease literature to outline existing perspectives, as well as to illustrate gaps in knowledge that may be filled by future social epigenetic research.

3.1 Ecosocial theory

Even prior to the emergence of social epigenetics, considerable work has attempted to link micro- and macro-level environmental influences with impacts on the body and subsequent outcomes related to health – much of this pioneered by early health geographers. A prominent example of this developed outside the discipline, but widely influential nonetheless, is ecosocial theory, proposed by epidemiologist Nancy Krieger to describe and explain the complex relationships that produce patterns of disease distribution among populations (Nancy Krieger, 2011b). Central to the ecosocial framework are concepts of embodiment and pathways to embodiment. For Krieger, embodiment refers to "how we literally incorporate, biologically, the material and social world in which we live, from conception to death" (Krieger, 2001, pg. 672). Pathways to embodiment, then, are theorized as being structured concurrently by societal power dynamics and arrangements of resources, property, and consumption, alongside the foundations of human biology shaped by evolution, ecological context, and personal histories (Krieger, 2001). Through these pathways of embodiment, an individual's trajectory of health and disease is closely linked to the internalization of their circumstances over the life course. Although Krieger's work has undoubtedly revolutionized the field of epidemiology in terms of integrating

social theory into understanding the manifestations of health and disease, it does not substantively address the mechanism(s) by which the social *becomes* biological and vice versa. Taking a social epigenetics approach could address this gap.

Although ecosocial theory provides a promising foundation on which to build social epigenetic studies, limitations remain, particularly in the context of the intersectional expression of chronic disease. We illustrate this, for example, using cardiovascular disease, in which symptoms of cardiac arrest appear differently in women versus men (Arslanian-Engoren et al., 2006), or autoimmune diseases such as systemic lupus erythematosus (SLE), in which as many as 90% of those affected are women, with women of colour disproportionately represented (Kinsey et al., 2018). Recognizing this, health-related disciplines have been urged to incorporate sex-and-gender-based analyses into their work (see CIHR: https://cihr-irsc.gc.ca/e/49347.html). While sex refers to a biological state dictated by the presence of chromosomes (i.e. male/female), gender is a socially constructed concept (Clayton & Tannenbaum, 2016). As conceptualizations of gender can be complex (Connell, 2012), here, we refer to gender broadly as an identity comprised of social, environmental, cultural, and behavioural factors and choices which pattern and influence health and ill-health (Clayton & Tannenbaum, 2016; Moss, 2002). Indeed, aspects of both sex and gender cannot be neglected when employing a biosocial analysis. In the ecosocial framework, Krieger (2011) does account for gender as well as other social identities such as race and class; however, these are treated as separate and distinct categorizations. As learned from feminist theorizations of gender and the body, identities cannot simply be added and subtracted; they inform one another and are inextricably entangled (Dyck, 2003; Moss & Dyck, 2003; Valentine, 2007). Moreover, these unique and entangled identities then inform individuals' experiences in places and over time; this becomes a key concern for theorizations of

embodiment and social epigenetics (Mansfield, 2012). In order to meaningfully take sex and gender into account, as well as related issues of race, class, and other social identities, social epigenetics must thus adopt a more intersectional approach (Crenshaw, 1991). To meaningfully integrate intersectionality into biosocial studies measuring changes at the molecular level, therefore, remains a considerable theoretical challenge.

3.2 Life course approaches

Life course approaches have been adopted in studies of chronic disease to theorize and explain how physical, social, and other environmental exposures during particular periods of life may have long-term effects on health and disease risk (Barker, 1995; Ben-Shlomo & Kuh, 2002). These studies often examine one or more types of biosocial pathways in this process, including behavioural, psychosocial, or biological (Ben-Shlomo & Kuh, 2002). Life course approaches operate with particular attention to time, as potential exposures are thought to have differential impacts on the body according to the stage of development (Lynch & Smith, 2005). Within this literature, emphasis is placed on exploring critical periods within the life course when the body is deemed more susceptible to environmental influences, such as when the body is rapidly growing or changing (Ben-Shlomo & Kuh, 2002). During critical periods, exposures are thought to have impacts on health that are greater in magnitude and longer-lasting compared to non-critical periods. Similarly, sensitive periods represent temporal windows where exposures have increased effects compared to baseline, but to a lesser extent than critical periods (Lynch & Smith, 2005). Although exposures have the potential to trigger change in any direction (i.e. with respect to epigenetics, increased or decreased expression), many life course models use an

accumulation of risk approach, whereby the total effects of exposures are added over the life course (Lynch & Smith, 2005).

Using a life course perspective, Blane et al. (2013) suggest a framework for testing pathways of how the social becomes biological. More specifically, this framework considers structural, behavioural, and interpersonal processes that shape health and disease, and the biological processes impacted by them – explicitly naming, as one of these, epigenetics. The proposed framework puts forth three premises: first, it recognizes that both social and biological processes can accumulate and interact. Second, it considers the relative importance of exposures according to life course age and/or critical or sensitive periods. Third, it accepts that exposures can drive biological processes in either positive or negative directions. While this framework suitably addresses the social and biological processes appropriate for social epigenetic analyses, it remains limited in that its references to "social-biological transitions" imply a unidirectional movement from social to biological. Drawing on feminist geographical studies of women living with chronic disease, we know that this relationship is more complex – it is not only bidirectional, but iterative and cyclical (Moss & Dyck, 2003).

For example, women with chronic autoimmune conditions found that as their health conditions worsened, their social circles deteriorated in tandem – hence "shrinking lifeworlds" of chronic disease (Crooks, 2007). For patients living with systemic lupus erythematosus (SLE) in Canada, while place-based experiences of the disease varied, their chronic illness inevitably resulted in the burden of many "lifecosts" – experiences of the direct and indirect economic costs and beyond (e.g. changing relationships; loss or change of work, volunteerism, and/or social participation) – which shaped future opportunities and, thus, social and environmental interactions (Dixon et al., 2022). These examples illustrate how just as the *social* becomes

biological, the *biological* becomes *social*; often concurrently and always contemporaneously *in place*. Given marked disparities in prevalence of such chronic conditions in women and disproportionately worse outcomes for minorities and women of colour (Kinsey et al., 2018), this also calls into question the impact(s) of gender roles and intersecting identities in mediating biosocial relationships in the context of time. Here, time refers not only to critical and sensitive periods, as characterized by the life course literature, but also encompasses various stages of life as well as the social, political and cultural contexts associated with a particular time-space.

Although life course approaches outline an attractive perspective for investigations of social epigenetics over time, the brevity of molecular processes may warrant greater attention to the dynamism and bidirectionality of biosocial systems and place-based experiences.

Theoretical challenges remain. First, even if epigenetic patterns are uncovered among social groups, epigenetic changes may not necessarily have discernable health consequences. The study of epigenetic modifications and their impacts at the cellular level remains early, and much about the genome and the epigenome is unknown (Feil & Fraga, 2012). As the consequences of epigenetics remain unknown, so too does the significance of epigenetics in contributing to the development of chronic diseases at large. Heeding back to Krieger's metaphor of the "web of causation", it is likely that epigenetic changes are merely one more strand of the web rather than the actual spider (Krieger, 1994). As we aim to connect biology and society, more attention to understanding the impacts of sex and gender on health is required. To date, while biological and epidemiological studies have begun to consider sex, they have engaged little with the complexity of gender and/or related intersectionalities (Clayton & Tannenbaum, 2016; Springer et al., 2012).

4. Methodological support for social epigenetics

An intrinsic feature of theory is its ability to shape other aspects of the research process, i.e., epistemology and methodology. Due to the transdisciplinary expertise required and the theoretical challenges presented by social epigenetics, methodological support for this line of inquiry remains minimal. Although there is no collective consensus regarding how to direct and undertake social epigenetics, the discussion of possibilities remains lively within health geography and beyond (seeL Chung et al., 2016; Cunliffe, 2016; Feil & Fraga, 2012; Prior, Manley, & Sabel, 2019). This section will outline some of the main methodological discussions and challenges facing social epigenetics, and assess the potential for each to provide meaningful contributions to the existing knowledge base.

Before conversations of a social-epigenetic axis, the field of epigenetics was – and remains – dominated by biologists seeking to uncover how environmental conditions are empirically related to changes in gene expression. As such, nearly all of the existing literature concerning epigenetics is quantitatively-focused in the positivist fashion of basic science (Cavalli & Heard, 2019). Although substantial progress has been made in our understanding of epigenetic mechanisms in the decades since their discovery, considerable knowledge gaps remain. Our lack of understanding about the vastness of the epigenome in combination with the temporally-sensitive and dynamic nature of these changes raises many methodological questions. Despite this, health geographers, biologists, and researchers in other fields have made several attempts to theorize how these transdisciplinary studies might best be undertaken.

4.1 Epigenome-wide association studies (EWAS)

Drawing largely on biological studies of epigenetics, perhaps the most widely-proposed methodology for investigating social epigenetics is epigenome-wide association studies (EWAS) (Vineis, 2018). For many years, biologists have undertaken genome-wide association studies (GWAS) in which the entire genomes of selected populations are scanned to look for phenotypic associations. Using the same principles, in EWAS studies, the epigenome (i.e. totality of epigenetic modifications within an individual's DNA) would be examined for similarities and/or patterns among and between selected groups. This methodology has been widely established in the scientific literature – for example, DNA methylation of particular genes involved in biochemical stress pathways have been linked to increased risk of chronic diseases such as mental health disorders, Alzheimer's, cardiovascular diseases, and some cancers (Shields, 2017).

In the context of social epigenetics, the populations under inquiry would be delineated according to social groups and/or conditions related to the social determinants of health. Recently, this methodology has begun to be put into practice. For example, in a longitudinal-based prospective birth cohort, particular epigenetic patterns were found among those with low socioeconomic status in childhood and/or absence of a parent in childhood, among other environmental conditions (McDade et al., 2017). Moreover, these patterns were correlated with elevated inflammatory profiles, a risk factor for many chronic diseases later in life (McDade et al., 2017).

A similar iteration of this methodology is to connect factors underpinning the social determinants of health with molecular changes in DNA methylation age (Prior et al., 2019; Vineis, 2018). DNA methylation age refers to the level of methylation in particular spans of the genome and is used as an indicator of biological age (Vineis, 2018). For example, a high DNA

methylation age would indicate a greater degree of cellular aging, resulting in decreased effectiveness of bodily function and poorer overall health. There is some support for this methodology. At least one cohort study drawing on this approach has revealed that low socioeconomic position is correlated with accelerated DNA methylation age compared to actual age (Fiorito et al., 2017); these results are hypothesized to be mediated primarily by deprivation and stress and were termed *embodiments of social position*.

Although these types of studies offer interesting insights, they are not without limitations. First, they rely on positioning populations into fixed and static categories. When it comes to biological attributes such as age or the presence/absence of disease, this may be appropriate; however, when it comes to dynamic and intersecting identities such as race, gender, education level, and/or socioeconomic status, this becomes much more challenging. As mentioned previously, identities are fluid and intersecting (Dyck, 2003; Moss & Dyck, 2003). With respect to sex and gender, while many regard sex as a fixed variable, its entanglement with socially-constructed gender identities cannot be ignored when making connections to the broader social environment, and an individual's experiences and interactions. With respect to race, biosocial researchers must exercise due caution – some social scientists have advised that separating individuals into racial groups in biologically-motivated studies runs the risk of reigniting the now-defunct field of race science (Meloni & Müller, 2018). It is not enough to perform our studies with distinct social variables; when it comes to social systems, we must be prepared to also consider how these multiple factors and identities transect to produce unique experiences that are neither interchangeable nor quantifiable.

4.2 Environment & the Exposome

Drawing on ecosocial and life course perspectives, and bridging these with conceptualizations from the geographical literature, health geographers have attempted to theorize the biosocial mechanisms of disease through environmental epigenetics (Guthman & Mansfield, 2013) and developing an exposomic health geography (Prior et al., 2019). Herein, the exposome encompasses the sum of every instance and type of exposure an individual is exposed to over their life course. Health (or ill-health) is thus theorized as the direct result of these exposures and the associated biological processes, taking into account the dynamic nature, potential overlap and interaction, and timing of exposure forces.

Exposomic health geography has been proposed as a way to close two identified theoretical gaps: first, how places directly influence health over time, and relatedly, plausible biological mechanisms for the embodiment of place (Prior et al., 2019). Central to this perspective is that all types of exposures, whether physical, social, or environmental, cannot be separated from the context in which they occur. Drawing on ecosocial theory (Krieger, 2011), this may include social, economic, political, and cultural structures, and the interactions that occur within them. Epigenetics in particular can be posited to mediate these relationships as epigenetic modifications at the cellular level are plastic and dynamic (i.e. context-dependent), temporally sensitive (i.e. critical and sensitive periods), and heritable (i.e. transmitting health inequalities over generations) (Prior et al., 2019). Therefore, epigenetics provides a functional mechanism through which place-based factors are embodied biologically. Current studies of the exposome have largely focused on biological or chemical exposures (Prior et al., 2019), but through operationalizing the geographical concept of place, this line of inquiry may be extended to encompass broader social and political contexts.

Exposome studies avoid many of the criticisms of EWAS and biologically-based social epigenetic methodologies as they focus on individuals rather than populations. Proponents have suggested operationalizing these approaches by prospectively recruiting participants and using GPS technology to track them over time (Prior et al., 2019). It is thus implied that this geospatial data would reveal momentary exposures to social and environmental phenomena (Prior et al., 2019).

While the exposome aims to capture all exposures over the life course in theory, researchers acknowledge this is certainly difficult if not impossible in practice (Prior et al., 2019). Even if tracking were to collect perfect data from the time of commencement, any exposures prior to implementation of the study, including the ever-important early life window, cannot be accounted for. As such, it has been suggested that it might be more poignant to draw from theorizations of critical and sensitive periods and take measurements during particular life stages. Thus, while exposomics represent a promising and active area for health geographers, its applicability for the practical undertaking of social epigenetic studies remains yet to be determined.

4.3 Qualitative and mixed methods

While qualitative and/or mixed methods epistemologies would serve to address the methodological challenges of social epigenetics, their discussion is absent from this literature. This may perhaps be because the field has been largely pioneered by biologists working in the positivist paradigms of basic science who have not been trained in the social sciences, and therefore, pay little or no regard to the impacts of daily life experiences on the molecular makeup of individuals. In a critique of such reductionist approaches, Chung et al. (2016) observed that

"what is common to all epigenetic studies with humans… is the absence of individual experiences as one of the key environmental factors" (pg. 176). This is a common pitfall in studies of chronic disease; for example, studies of cardiovascular disease, one of the most globally prevalent and commonly studied chronic conditions, have rarely taken advantage of qualitative methods to date (Mcilvennan et. al., 2019). In instances where qualitative methods are integrated, they are typically used for intervention evaluation or policy analysis rather than investigations of disease development or illness experience.

Social scientists propose that social epidemiology, and particularly social epigenetics, would benefit from integrating qualitative analysis into their methodological frameworks (Cutchin, 2007). Aside from allowing the theoretical space for dynamic interactions and the complexities of individuals and their environments (Prior et al., 2019), the use of qualitative methods also allows for a broader definition of health and wellbeing. Rather than correlating environmental factors and individual experiences with static measures of disease risk, we open up the conceptual space to account for perceptions of lived experiences, which may extend even beyond researchers' (culturally-informed) definitions of health, and what can adequately be captured using quantitative methods such as surveys or questionnaires. For some, these views might even be directly tied to features of the environment (i.e. Indigenous conceptualizations of health; see Richmond & Ross, 2009; Richmond et al., 2005), rather than simply informed by them. Similarly, the use of qualitative methods allows for expanded views of gender that transcend traditional binaries, encompassing non-binary and gender non-conforming identities, among others.

Moreover, this could provide a window to not only investigate what is associated with negative health outcomes, but what might promote positive health outcomes. The strengths of

integrating qualitative methods in investigations of chronic disease can be seen, for example, in epidemiologic studies of myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS), in which researchers concluded that "analyses were richer and… findings ultimately more impactful when we integrated qualitative and quantitative methods" (Jason & Reed, 2015). These authors subsequently stated that not only were they able to better understand social and community context surrounding these illnesses – an important aspect for understanding social epigenetic patterns - but their findings were better able to give voice to patients and more applicable for policy translation (Jason & Reed, 2015).

The operationalization of qualitative methods in a largely positivist space does require some consideration as to how these methods can be meaningfully integrated. Key to a mixed methods approach is a purposeful study design that privileges both quantitative and qualitative approaches to understanding (Cresswell & Clark, 2017). To this end, we propose a mixed methodology for social epigenetic investigations that provides a more holistic view of biosocial interactions. For example, in this study design, a population of interest would be identified along with representative controls. The quantitative arm of this type of study might involve EWAS or DNA methylation age analyses, and would be complemented by a more qualitative arm of studies involving in-depth interviews and/or survey data. Through concurrent analyses, we are able to explore both "the what" (i.e. potential epigenetic patterns) as well as the "why" and "how" (i.e. in-depth perspectives and experiences of an individual's environment) (Brown et al., 2015). Thus, through mixed methodologies, a more holistic and nuanced snapshot of these biosocial pathways could be revealed. Although qualitative and mixed methodologies have clear limitations, such as a notable a lack of rigour in some contexts (Baxter & Eyles, 1997; Brown et

al., 2015; Onwuegbuzie, 2006), we argue that this represents an opportunity for future work in social epigenetics rather than a real constraint.

4.4 Integrated knowledge translation

Throughout this paper, we have argued that social epigenetics represents a unique area of research that is *necessarily* transdisciplinary. Indeed, the criticality of not only integrating, but fully merging biological and social science approaches is evident in examining the theory and methodology to underpin these types of studies. However, for investigations to be truly transdisciplinary, we further advocate for the inclusion of knowledge users throughout the research process. Firstly, knowledge users – in the context of chronic disease, these may be patients, physicians, care takers, or others involved in healthcare or policy – bring a unique vision of how to ground research in reality and useability. These perspectives maintain accountability for researchers to demonstrate how study results will be applied and used. Knowledge users also impart important wisdom for the research dissemination process. This is particularly pertinent to social epigenetics studies, which will undoubtedly be conceptually and methodologically complex. It is becoming especially clear in health research, and research more broadly, that research done "on" vulnerable and marginalized populations is being replaced in favour of research done "with" members of these groups. Not only does this create opportunity for researchers to rebuild oppressive systems and mobilize promises towards equity, diversity and inclusion in academia, but importantly, strong and active partnerships with knowledge users may yield richer, more meaningful, and translatable study results (Cardwell et al., 2020; Dixon et al., 2022). Given the insights social epigenetics stands to contribute to our understanding of health inequalities and the development of complex chronic diseases, health geographers are

uniquely positioned to build upon this foundation and continue to engage in new knowledge translation initiatives that not only promote, but are effective in improving, the health of (particularly vulnerable) populations.

5. "New wine" and a role for health geographers

This paper has demonstrated that the emerging field of social epigenetics is more than just old wine in new bottles. While conceptual frameworks in the social sciences typically ignore the nuances of biology, basic science and epidemiology remain largely atheoretical and lack recognition of the roles of structure and agency in health (Daniel et al., 2008; Nancy Krieger, 2011b). Perhaps the most significant contributions of social epigenetics will be theories and methods that transcend disciplinary boundaries, such that investigations into the causes and consequences of health outcomes for individuals is rendered truly transdisciplinary (Elliott, 2011); but health geographers have been occupying this ontological space for some time and this is fruitful soil for germination of subsequent new epistemologies and methodologies. Indeed, health geographers have enjoyed a legacy of conducting investigations that work to dissolve traditional disciplinary barriers and occupy the theoretical and substantive spaces between them (Cloke & Johnston, 2002). As a robust area of research that draws on thinking from many others, both health-related and beyond, health geography thus represents an ideal space to explore these transdisciplinary ideas (Elliott, 2011) and also provides a foundation for researchers in disparate disciplines to come together, share their expertise, and collaborate in a meaningful way across traditional arbitrary divides.

Our discussions of social epigenetic theory and methodology have, not coincidentally, raised issues of space, place, time, and scale. Indeed, this emerging area presents new ways for

health geographers to engage with these touchstone concepts. Investigations of biosocial pathways force researchers to grapple with the liminal spaces *between* environment and health. This conceptual space may be relative, absolute, or social; it also relates to individuals' movements through space and time. For social epigenetics, researchers must reconcile the theoretical space between environments and bodies, bodies and genes. This nexus also opens up new possibilities for a deeper understanding of the embodiment of place-based experiences.

Health geographers have long been concerned with the relationship between health and place (Kearns, 1994; Kearns, 1993; Kearns & Moon, 2002). Social epigenetics, in particular, provides opportunities to empirically measure the bodily impacts of place-based experiences, and their connections to disease and illness. Time also raises important questions, especially when social epigenetics are viewed from a life course perspective, which prioritizes critical and sensitive periods. The transience and temporality of epigenetic changes and gene expression, as related to the magnitude of their impacts on health, have implications for policy and intervention – these issues remain largely out of focus for basic scientists, creating a niche for collaborative and complementary work.

Recently, health geographers have begun to delve inside the body, for example, engaging with the microbiome (Lorimer, 2017) and other "omics" (Stallins et al., 2016). Social epigenetics takes us further yet, to arguably, the smallest scale. Prospective social epigenetic studies aim to connect macro-level environmental phenomena to molecular-level health effects. As such, new conceptualizations and examinations of scale in health and disease are required; a role that health geographers are uniquely positioned to fill.

Similar to the discipline's close relationship with theory is its alignment with critical perspectives and the pursuit of social justice. It may be a double-edged sword that social

epigenetics stands to reveal the biological implications of social inequalities in health. Naturally, it is the hope of researchers that revealing the embodiment of health inequalities will translate to policies that move toward better health for all. However, some have raised concerns that such studies may bolster the disproven and estranged field of race science (Meloni & Müller, 2018). As such, it is essential that social epigenetics research is pursued only with an ethically sound deep awareness of social context. Drawing on critical perspectives and heeds from Rosenberg (2014, 2017), health geographers should proceed in due course focusing their efforts on the most vulnerable and marginalized and ensure that research results benefit the oppressed rather than their oppressor (Katz, 1994). Social epigenetics is poised to offer insights into socially-sensitive phenomena such as intergenerational trauma, and as such, health geographers should remain at the forefront to ensure that studies are not only meaningful, but actionable.

6. Conclusions

The advent of molecular technologies has marshalled in new ways of thinking about human-environment interactions, and their implications for health and disease risk. The field of epigenetics has recently taken a sociocultural turn toward "social epigenetics". In exploring the existing biosocial literature as well as the insights social epigenetic research stands to uncover, we contend that social epigenetics indeed represents a novel space to conduct genuine transdisciplinary inquiry.

Through assessing the theoretical and methodological support for this area of research, it is evident that while some foundational pieces exist, further elaboration is needed. In the context of chronic diseases, which are highly complex in their development, manifestations, and interactions with the environment, both theoretical and methodological attention is required to

meaningfully integrate understandings of gender and intersectionality. While methodologies exist in the biomedical realm to conduct epigenetic studies, it is critical that equal consideration be given to the complexity of social systems. To this end, we propose integrating qualitative methods with traditional laboratory-based methodologies.

Given the content at hand, and the gaps that exist, health geographers are uniquely positioned to take on these challenges and participate in this paradigm-shifting work. Drawing on health geography's history, foundational concepts, multiplicity of methods, and commitment to critical and theoretical perspectives, social epigenetics stands much to glean from this robust and impactful discipline. Drawing on the similarly emerging area of knowledge translation, health geographers can use the conceptualizations and empirical data from social epigenetic studies to drive forward both the discipline, as well as real-world policy applications that enhance health for all.

CHAPTER FOUR

Manuscript #2: Towards an understanding of the biopsychosocial determinants of CVD in SLE: A scoping review

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Abstract

Objective: Systemic lupus erythematosus (SLE) is a chronic autoimmune condition with significant physical, mental, psychosocial and economic impacts. A main driver of SLE morbidity and mortality is cardiovascular disease (CVD). Both SLE and CVD exhibit disparities related to gender, race, and other social dimensions that are linked with biological outcomes and health trajectories. However, the biospsychosocial dimensions of CVD in SLE populations remain poorly understood. The objective of this study is to systematically investigate the existing literature around the known social factors influencing the development of CVD among people with SLE.

Methods: A scoping review protocol was developed according to PRISMA-ScR guidelines. A search strategy was developed to encompass three main concepts: SLE, CVD, and social factors. Four databases were searched (PubMed, SCOPUS, PsychINFO, CINAHL) and 682 studies were identified for screening. Articles were screened in two phases (title/abstract and full-text) to determine whether they fulfilled the selection criteria.

Results: Seven studies were included after screening. All were conducted in the US between 2009-2017. Four studies (57%) were cross-sectional, and three (43%) were longitudinal. Most employed SLE cohort populations (n=6, 86%) and one drew from a national-level insurance database (n=1; 14%). We identified four main themes encompassing social factors:

socioeconomic status (SES) and education (n=4; 57%), race/ethnicity (n=5; 71%), mental health (n=2; 29%), and gender (n=2; 28%). Overall, low income, fewer years of education, Black race/ethnicity, depression, and male gender were all associated with CVD risk factors and outcomes in SLE.

Conclusions: While several social factors were identified as contributing to CVD in SLE populations, considerable gaps remain as many social determinants remain un(der)explored. There is rich opportunity to integrate social theory, advance conceptualizations of race/ethnicity and gender, expand investigations of mental health, and explore novel geographical contexts. In healthcare policy and practice, the identified social factors should be considered for SLE populations during decision-making and treatment, and patient education resources should be specifically targeted for these groups.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition resulting in autoantibodies that attack normally healthy organs and tissues. This ongoing inflammation causes a variety of clinical signs and symptoms, such as muscle and joint pain, extreme fatigue, UV sensitivity, and/or a characteristic butterfly-shaped rash. It is well known that SLE may be triggered by stressors which may be environmental (e.g., ultraviolet light) (Andrade et al., 2021) or psychosocial (e.g. post-traumatic stress disorder) in nature (Pawlak et al., 2003). In addition to these debilitating and unpredictable physical impacts, patients with SLE also face social limitations (Aim et al., 2022; Sloan et al., 2021), mental health challenges (Duca et al., 2022; Nikoloudaki et al., 2022), and a variety of direct and indirect economic "lifecosts" related to altered career trajectories, increased healthcare and treatment, and decreased quality of life (Dixon et al., 2022).SLE also affects predominantly young women (Danchenko, Satia, & Anthony, 2006). Additionally, non-white groups are disproportionately represented (Izmirly et al., 2021), with these patients often experiencing poorer clinical outcomes (Aguirre et al., 2023; Ugarte-Gil et al., 2023). Taken together, we characterize SLE as gendered, racialized, invisible, episodic, and idiosyncratic. As such, recent literature has begun to view SLE through a bio(psycho)social lens, an approach that considers the intersections of biology, psychology, and social systems in the production of health and illness (Kinsey et al., 2018).

A leading cause of morbidity and mortality for patients with SLE is cardiovascular disease (CVD) (Taylor et al., 2023); an estimated 27-52% of SLE-related deaths are due to CVD (Barber et al., 2021). A recent meta-analysis indicates that patients with SLE have at least a two-fold greater risk of CVD than populations without SLE, including significantly increased risks of atherosclerosis, myocardial infarction, peripheral vascular disease, and heart failure (Lu et al.,

2021). The increased incidence of CVD in SLE populations has been attributed in part to a number of inflammatory pathways promoting endothelial dysfunction (Taraborelli et al., 2018) and vascular stiffness (Montalbán-Méndez et al., 2018) including elevated levels of type I interferons (Tydén et al., 2017), low-density granulocytes (Knight & Kaplan, 2013), autoantibodies (Miyakis et al., 2006), and dyslipidemia (Smith et al., 2014), however, the specific etiology remains unclear.

In the general population, CVD is linked to social and structural determinants (e.g., poverty, education, neighbourhood, racism/discrimination) (Daniel et al., 2008; Harrington & Elliott, 2009; Powell-Wiley et al., 2022). These determinants have been shown to drive health behaviours and individual risk that lead to CVD, but are also increasingly recognized for direct biological impact as mediated by chronic stress (Osborne et al., 2020). Although SLE populations have significantly elevated risk of CVD events, the contributions of the socio-environmental context remain poorly understood. Recognizing this gap, we conducted a scoping review to explore and characterize how different social factors influence risk and outcomes of CVD in patients with SLE.

2. Methods

A scoping review was utilized for this broad research question that has yet to receive extensive attention in the literature. In contrast to other types of reviews, scoping reviews are useful for identifying the types of available evidence, how existing research was conducted, what key factors have been examined, and any outstanding knowledge gaps (Munn et al., 2018). We were guided by Arksey & O'Malley's (2005) methodological framework for conducting scoping

reviews in conjunction with the PRISMA-ScR guidelines (PRISMA extension for scoping reviews) (Tricco et al., 2018) to ensure transparency and rigour.

2.1 Patient & Public Involvement

Our research team includes a patient partner (CS) who has lived experience with SLE. Using a previously validated integrated knowledge translation (iKT) approach, our patient partner provided input and feedback on all stages of design, measurement and evaluation of this research, including the interpretation of results and manuscript preparation.

2.2 Search Strategy

A search strategy was developed in collaboration with a university librarian (JS) with extensive experience in conducting and publishing scoping reviews. The search string was developed based on three concepts: SLE, CVD and social factors. For each main concept, a list of relevant search terms was established (Table 1). The search terms for CVD were developed in collaboration with one of the authors (MC), a rheumatologist specializing in SLE. The search terms for social factors were developed based on the social determinants of health framework (Wilkinson & Marmot, 2003) supplemented by key references in the biopsychosocial literature (van der Kolk, 2015; Maté, 2003), or biopsychosocial studies focusing on SLE (Kinsey et al., 2018) or CVD (Daniel et al., 2008). The search strategy was iteratively reviewed by the research team.

Four databases were chosen based on their relevance to the biopsychosocial literature (e.g., subject matter is biology, health or social sciences): PubMed, Scopus, PsychINFO, and CINAHL. The four databases were searched from 2000-2022 to correspond with the initial

publication of the social determinants of health framework (Wilkinson & Marmot, 1998) and the time of searching. Articles were searched in English only due to the language proficiency limitations of the team. The search was limited to peer-reviewed journal articles only. Test searches were performed in conjunction with the librarian to identify and adjust or remove search terms generating non-specific results. A sample search strategy is detailed in Figure 1. Searches were conducted in July 2022. Studies identified by the search strategy were imported into Covidence software (www.covidence.org) and duplicate records removed.

2.3 Study Selection

A two-phase screening process was employed: 1) title and abstract screening, and 2) full-text screening. Title and abstract screening was conducted in duplicate by the first author and a research assistant using pre-determined selection criteria. Included studies were required to address all three of: SLE, CVD, and social factors and utilize an adult (>18 years) study population. Pediatric studies were excluded due to differences from adult SLE in etiology, experiences and health trajectories (Knight et al., 2016; Mina & Brunner, 2010; Tarr et al., 2014). Animal studies were excluded due to a lack of transferability with respect to social dimensions. Clinical case studies and reviews were also excluded, although the references of relevant reviews were screened for any additional studies not obtained from the initial search.

Screening was performed independently using Covidence and any conflicts were resolved by discussion with the research team. Full-text screening was conducted in duplicate by the first author and at least one other researcher from the team, with each researcher screening a minimum of two studies. Our patient partner participated in the process as a third screener with support from the first author. A decision was made to modify the selection criteria during full-

text screening to focus on "first order" social determinants (i.e. a social aspect of being), rather than "second order" determinants (i.e. a behaviour or state driven by social aspects of being). Thus, some previously included concepts (see Table 1) were excluded from the final analysis. This process is represented in the PRISMA chart shown in Figure 2.

2.4 Data Extraction

The data was charted using an extraction template from Covidence. The data was charted independently by the first author (ES) and reviewed by the research team. The following variables were sought during the charting process: country/region in which the study was conducted, theory/framework used, purpose/aim, study design, start/end dates, social variable(s) studied, operational definition(s) of social variable(s) studied, cardiovascular outcomes measured, population description, participant base/affiliation (e.g. universities, hospitals, other), participant inclusion/exclusion criteria, total number of participants, key findings, study limitations, study strengths, knowledge translation (KT) plan, and co-production of knowledge (i.e. whether knowledge users were included in the research process). Critical appraisal of individual sources of evidence was not performed (Munn et al., 2018) as this was a scoping review.

3. Results

The search resulted in 826 records, of which 144 duplicates were removed, leaving 682 studies for screening. After the first phase of title and abstract screening, 11 studies were eligible for full-text screening. Studies were excluded due to irrelevant variables measured (n=1), non-

CVD outcomes (n=1), or ineligible study design (e.g. intervention studies) (n=2). A total of seven studies were included for analysis. A summary of the charted data is included in Table 2.

3.1 Study descriptions

All studies included were conducted in the US between 2009-2017. Figure 3 illustrates the trend in publication of included articles over time: most in 2009 (n=2; 29%) and 2012 (n=3; 43%), with one each (14%) in 2010 and 2017 respectively.

Four studies (57%) employed a cross-sectional design, while the remaining three (43%) were longitudinal. Nearly all utilized existing SLE cohort populations (n=6; 86%) that were based in universities (n=3; 43%), hospitals (n=1;14%) or regional/city settings (n=2; 29%). The remaining study drew from a national-level insurance database (n=1;14%), reflecting a broader scale.

3.2 Study populations

Our selection criteria intentionally selected for study populations of adults > 18 years of age living with SLE. Confirmation of SLE diagnosis for participants was described by most studies (n=6; 86%), either by meeting at least four of the American College of Rheumatology criteria for SLE (n=4; 57%) (Aringer et al., 2019; Hochberg, 1997), meeting ICD-9 criteria for SLE (n=1; 14%) (CDC, 2020), or diagnosis by a cohort principal investigator (n=1; 14%). Four studies included both men and women (57%), while three were three were restricted to women only (43%). Other exclusions included patients with rheumatoid arthritis or scleroderma (n=1;14%), patients with a history of CVD (n=2; 29%), and patients who did not identify as either Caucasian or African American (n=3; 43%).

3.3 Social factors influencing CVD in SLE

We identified four themes encompassing social factors: socioeconomic status (SES) and education, race/ethnicity, mental health, and gender. Race/ethnicity (n=5; 71%) and SES/education (n=4; 57%) were the most frequently addressed in the context of CVD and SLE, followed by mental health (n=2; 29%) and gender (n=2; 28%).

3.3.1 Socioeconomic status (SES) and Education

SES is an important indicator of health, defined as the sum of an individual's combined economic and social status (Baker, 2014). Thus, SES comprises a number of factors including income, education, occupation/work, social class, relative poverty, etc. (Darin-Mattsson, Fors, & Kåreholt, 2017).

In a multivariate analysis of a multiethnic cohort by Pons-Estel et al. (2009), Patients with SLE with fewer total years of education were more likely to have cumulative cardiovascular damage defined as one or more of: (i) angina or coronary artery bypass surgery, (ii) heart failure and (iii) myocardial infarction lasting more than six months (OR=0.85). Similar results were reported by Greco et al. (2012), who found that total years of education (≤12 years or ≥12 years) were negatively associated with vascular disease (OR=0.80) assessed by the presence of subclinical coronary artery calcification and/or carotid artery plaque.

In an analysis by Maynard et al. (2012), both education and combined household income were associated with cardiovascular risk factors and outcomes in individuals with SLE, although this relationship was different for the racial/ethnic groups studied. Overall, the lowest income group (<$25,000 USD per year) were more likely to smoke tobacco (OR=2.31 for white; OR=3.64 for African American) and experience cerebrovascular incident (OR=2.85 for white;

OR=1.66 for African American). The lowest income group of white background were more likely to be obese (BMI >27.8 kg/m^2 for men; >27.3 kg/m^2 for women) (OR=1.65) and/or experience myocardial infarction (defined using SLICC damage index) (OR=3.24), while the lowest income African Americans had a higher frequency of hyperlipidemia (cholesterol >200 mg/dl) (p=0.04). When multivariate analysis was performed for the white patients with SLE, a significant graded relationship was observed between income and risk factors such as smoking, hypertension, hyperlipidemia, and diabetes (according to American Diabetes Association criteria), as well cardiovascular outcomes such as myocardial infarction and cerebrovascular incidents. While this relationship was not seen in the African American patients with SLE, lower income was associated with diabetes and smoking in this population.

3.3.2 Race/ethnicity

The findings by Maynard et al. (2012) described above found that while SES was indeed associated with CVD in SLE, this relationship was altered when stratified by racial/ethnic groups. Specifically, while the lowest income white group had an increased frequency of obesity, the lowest income African American group exhibited higher rates of hyperlipidemia. Building on these results, four additional studies examined such relationships.

In a study cross-sectional study of African American and Caucasian women with SLE, Rhew et al. (2009) found that African American women with SLE were more than twice as likely to have subclinical carotid plaque than their white counterparts, and had significantly higher levels of lipoprotein A and C-reactive protein in the blood. Furthermore, they had higher blood pressure, corticosteroid use, disease damage (measured by SLICC Damage Index) and disease activity (measured by SLEDAI), all of which increase overall risk for CVD.

Scalzi et al. (2010) found similar results in their cross-sectional study of racial disparities in age at cardiovascular events and/or CVD-associated hospital death. White patients with SLE were significantly older than Black, Hispanic, and Other racial groups at the time of cardiovascular events and/or related deaths, although this relationship was not significantly different between the white and Asian groups (mean age at CVD-related death = 67.1 years for white; 52.8 for Black; 62.0 for Hispanic; 63.8 for Asian; 63.5 for Other). The greatest disparity was between white and Black SLE populations, as Black patients with SLE were, on average, 9.6 years younger at the time of hospitalization for CVD. When categorized by age group, 55% of Black women with SLE were admitted to hospital for CVD in the youngest age group (<55 years), compared to 41% Hispanic women, 33% Asian women, and 26% white women with SLE. Overall, Black race was independently associated with poorer health trajectories and outcomes in the context of SLE and CVD.

In a cross-sectional study of both men and women with SLE, Tan et al. (2012) found that African American men were more likely to have cardiovascular damage, as assessed by both laboratory and clinical features, than white men.

Only one study found no association between Hispanic, African American or Caucasian race and cardiovascular damage in a longitudinal SLE cohort (Pons-Estel et al., 2009).

3.3.3 Mental health

Two studies investigated the relationship between mental health, specifically depression, and the progression of subclinical vascular disease among individuals with SLE.

In a cross-sectional study, depression was more prevalent among women with SLE and vascular disease as compared to those without vascular disease (Greco et al., 2012). Those

patients with SLE with depression had nearly 4-fold greater odds of vascular disease and this was independent of traditional risk factors. Given that these relationships remained relatively unaltered after adjusting for other covariates, the authors concluded that depression has an independent role in the development of CVD in SLE.

A similar study revealed that depression was associated with increased progression of carotid intima-media thickness over the next five years in the SLE group, independent of traditional risk factors (Jorge et al., 2017).

3.3.4 Gender

Two studies referenced gender as a variable; both found that men with SLE experienced more frequent and severe CVD outcomes than women. While Pons-Estel et al. (2009) found that male gender was independently associated with cardiovascular damage ($p<0.0006$), Tan et al. (2012) found that men were more likely to have hypertension as a risk factor (OR=1.8), as well as cardiovascular outcomes such as angina (OR=2.2), myocardial infarction (OR=2.5) and venous thrombosis (OR=2.9).

4. Discussion

Four broad social themes emerged from this scoping review in connection to CVD in SLE: socioeconomic status/education, race/ethnicity, mental health, and gender. Specifically, low income, fewer years of education, Black race/ethnicity, depression, and male gender were all associated with the development of cardiovascular risk factors and outcomes. Other social determinants of health found in the Marmot framework (Wilkinson & Marmot, 2003) – including stress, early life, social exclusion, work, unemployment, social support, substance use, food

security, transport, housing, political conflict, and health services access – though interconnected with the identified themes - were not directly addressed in the literature in the context of SLE and CVD.

All studies employed a quantitative methodology. None described a theoretical framework, inclusion of knowledge users, or other knowledge translation approaches, although all did address the clinical implications stemming from their results. There is clear opportunity for future studies to expand this line of inquiry by first integrating social theory. As Nancy Krieger reminds us, without theory observation is blind and explanation is impossible (Krieger, 2011b). In addition, a more comprehensive story of CVD and SLE could be told using qualitative and/or mixed methods. Innovative qualitative methodologies such as oral histories and photovoice are unique lenses into the complex web of factors shaping chronic illness (e.g. (Tsui & Starecheski, 2018; Yi-Frazier et al., 2015). Furthermore, the involvement of knowledge users in the production of knowledge has been shown to effect greater change – and better science – given regular input into the research process (Dixon & Elliott, 2019; Nguyen et al., 2020). This is indeed the strategy used by the research team undertaking this scoping review.

Four studies examined the relationships between SES, SLE, and CVD, and three of these studies were in accord that low SES increases risk of CVD. Notably, all four studies used education as an indicator of SES, and only one utilized measures of income. These findings are unsurprising, given the associations of low SES with poorer SLE outcomes over the disease course (DeQuattro & Yelin, 2020) and similar relationships demonstrated among other chronic conditions (e.g. Gershon, et al., 2012; Kivimäki et al., 2020; Shoham et al., 2005).

Race/ethnicity was the most widely studied theme and while racialized individuals with SLE were all at higher risk of CVD than white SLE groups, African American and Black

populations consistently fared worst. This is in line with similar investigations of racial inequities morbidity and mortality in pregnancy (Minehart et al., 2021), cancer (Yedjou et al., 2019), and COVID-19 (Mackey et al., 2021), among others, in the general population. In SLE, these results may be in part due to these individuals experiencing greater SLE-related organ and tissue damage (Maningding et al., 2020), but likely also reflect the systemic racism experienced by these groups both in healthcare systems (Hamed et al., 2022) and societally (Ford, Williams, & Kue, 2021; Paradies et al., 2015). In contrast to its widespread investigation, there was little clarity in how race/ethnicity was defined and operationalized, nor was there discussion of both race and ethnicity as social constructs "without scientific or biological meaning" (Flanagin et al., 2021). The exploration of racial/ethnic identities was also limited: of the studies that included race and/or ethnicity as a variable, three restricted their analyses to African American and white participants only (Maynard et al., 2012; Rhew et al., 2009; Tan et al., 2012). Two additional studies expanded this to include Hispanic populations (Pons-Estel et al., 2009; Scalzi et al., 2010) and only one included categories for Asian/Pacific Islander and 'Other' (Pons-Estel et al., 2009). A notable gap was representation of Indigenous Native American populations, for whom SLE is more common and more severe (Kheir et al., 2018), and whose experiences are further compounded by the intergenerational impacts of colonization and resulting barriers to healthcare access (Cromer, Wofford, & Wyant, 2019; Liddell, 2020). Future studies should address these gaps, and endeavour to: i) adopt more nuanced definitions of race and ethnicity (Flanagin et al., 2021); ii) broaden analyses to additional racialized groups, including individuals identifying across multiple minority groups (Liebler & Halpern-Manners, 2008); and to this end, iii) engage with theories of intersectionality (Crenshaw, 1995; Holman et al., 2021).

Although two studies reported gender differences in the development of CVD in SLE, the results remain somewhat inconclusive as it is unclear whether the variables studied were, in fact, self-identified or self-reported gender - a social construct - or biological sex. Given the established links between SLE and female hormones (Christou et al., 2019), there are likely to be sex-based differences; however, the role of gender is more convoluted. Future studies could address this through adopting broader views of gender outside of the gender binary, and how this influences SLE and/or CVD experiences and health trajectories. As outlined above, future socially-rooted studies should draw on feminist theorizations of intersectionality (Springer et al., 2012) to better account for the effects of gender in conjunction with other concomitant identities. Nonetheless, these study findings report that, importantly, men with SLE are at particular risk for CVD, delineating important implications for clinical practice.

It has been well established that patients with SLE face a number of mental health challenges, which may reflect neuropsychiatric manifestations of the condition (Fujieda, 2020) or psychosocial stress (Meszaros, Perl & Faraone, 2012). Although two studies explored this theme, the only mental condition examined was depression. Patients with SLE are indeed at higher risk of developing depression than the general population (Palagini et al., 2013), and the literature has established links between depression and CVD in other contexts (Atlantis et al., 2012; Silverman, Herzog, & Silverman, 2019). However, individuals living with SLE are also particularly vulnerable to developing anxiety (Zhang et al., 2017), cognitive impairment, and other mental disorders, which are associated with heightened morbidity and mortality from CVD. These relationships should additionally be explored to support better prediction of risk, as well as to inform screening, intervention and treatment.

All of the studies included for the analysis were based on the US and utilized American populations. There was some geographic variation across the country, as studies drew on SLE cohorts primarily from the northeast (Greco et al., 2012; Jorge et al., 2017; Maynard et al., 2012; Rhew et al., 2009; Tan et al., 2012), with some representation from southern states (Pons-Estel et al., 2009), as well as a national sample from an insurance database (Scalzi et al., 2010). Taken together, this set of studies provides some insight into how these effects pervade distinct environments with their own social structures, geo-political influences, and cultural norms. However, such social systems and influences are necessarily shaped by place and as such, may have differential effects based on the context. Furthermore, SLE is a demonstrated global health issue, affecting individuals worldwide (Barber et al., 2023; Tian et al., 2022). Thus, the expansion of similar research into novel geographical settings is needed.

A notable limitation of the selected studies is that while important connections are made between the social environment, SLE, and cardiovascular disease, insight into the causal mechanisms of this interplay remain to be elucidated. There is growing interest in social epigenetics, chronic stress, and allostatic load (Kinsey et al., 2018; Peterson, 2020; Saban et al., 2014) as possible mediators of these processes. While current evidence demonstrates how acute and chronic stress promote inflammatory atherosclerotic processes (Osborne et al., 2020), these processes are not yet well understood, and additional work is required to disentangle these systems in the context of SLE.

This scoping review has several strengths. Firstly, the search string developed captures not only the established social determinants of health (Wilkinson & Marmot, 2003), but other important CVD determinants reported in the bio(psycho)social literature (Daniel, Moore, & Kestens, 2008; Kolk, 2015; Maté, 2003). Given our iKT approach, a transdisciplinary team of

experts – including an SLE physician and patient partner – provided input and feedback at all stages of the research process, including identifying other contributing factors to add to the search strategy. Including knowledge users on our research team was effective in both developing a robust study design, but perhaps more importantly, ensuring that our research results were useful, useable, and meaningful (Dixon & Elliott, 2019). As our review was guided by an established framework (Arksey & O'Malley, 2005) and PRISMA-ScR guidelines (Tricco et al., 2018), we have ensured rigour and reproducibility.

There are some limitations as well. First, due to the language abilities of the research team, our search was limited to articles in English only, therefore, it is possible that additional articles in other languages and contexts were not accessible. Due to the timing of data collection and analysis, any articles published past 2022 were not included. Studies examining pediatric SLE were also excluded from the dataset as these conditions exhibit different etiologies (Chung et al., 2007; Mina & Brunner, 2010; Pons-Estel et al., 2017); therefore, these patients are not represented in the analysis. Lastly, although every effort was made to ensure the robustness of our search, some relevant articles may not have been captured due to the keywords and/or filters used.

5. Conclusions

As CVD is the leading cause of death for patients with SLE, there are important implications for policy and practice. Those with SLE who are men, belong to racialized groups, have low SES/education or live in low SES regions, and/or have a history of depression are at particular risk of CVD and should be targeted by healthcare professionals for early preventative therapy and risk monitoring. In line with the most recent guidelines from the American College

of Cardiology, these characteristics should be considered as "risk enhancing factors" in clinical practice, and inform decisions about treatment for at-risk individuals (Arps, Blumenthal, & Martin, 2018). Moreover, patient education initiatives about the risks of CVD and evidence-informed management strategies should be developed and tailored towards these groups. Identifying at-risk SLE populations may also be an effective step towards developing social interventions, in line with recent advances in social prescriptions (Bird et al., 2020; Mercer, 2018), to reduce morbidity and mortality and increase quality of life for those living with SLE.

From a research perspective, there is much work to be done; work that employs alternative epistemologies, is theoretically informed, and in partnership with knowledge users.

Acknowledgements

We gratefully acknowledge Jackie Stapleton, Librarian at the University of Waterloo for her expertise and guidance on developing the scoping review search strategy.

Tables & Figures

Table 1. Search concepts and key words. The following table lists the three primary concepts and keywords used to develop the search strategy and resulting search string.

LUPUS	SOCIAL FACTORS	CARDIOVASCULAR DISEASE
	General terms	
Lupus		Coronary heart disease
SLE	Social factors	Coronary death
Systemic lupus erythematosus	Social determinants	Coronary insufficiency
	Social environment	Coronary artery bypass graft
	Social conditions	Coronary procedure (e.g. bypass, stent)
	Social gradient(s)	
	Social inequities/inequalities	Percutaneous coronary intervention
	Social determinants of health	Angina
		Cerebral infarction
	Income	Myocardial infarction
	Social protection	Transient ischaemic attack (TIA)
	Finances	
	Financial need	Ischaemic stroke
	(Socio)economic status	Ischaemic heart disease
	Education	Cerebrovascular events
	School*	Cerebrovascular accidents
	Degree*	Stroke
	College/University	Peripheral artery disease
	Unemployment/Non-employment	Peripheral vascular disease
		Heart failure
	Job (in)security	Congestive heart failure
	Work/job/career	ST elevation
	Food (in)security	Non-ST elevation
	Nutrition**	Occlusion and stenosis of carotid artery
	Diet**	
	Housing/House/Dwelling	Claudication
	Environment*	
	Neighbourhood	
	Early childhood/life	
	Social inclusion/exclusion	

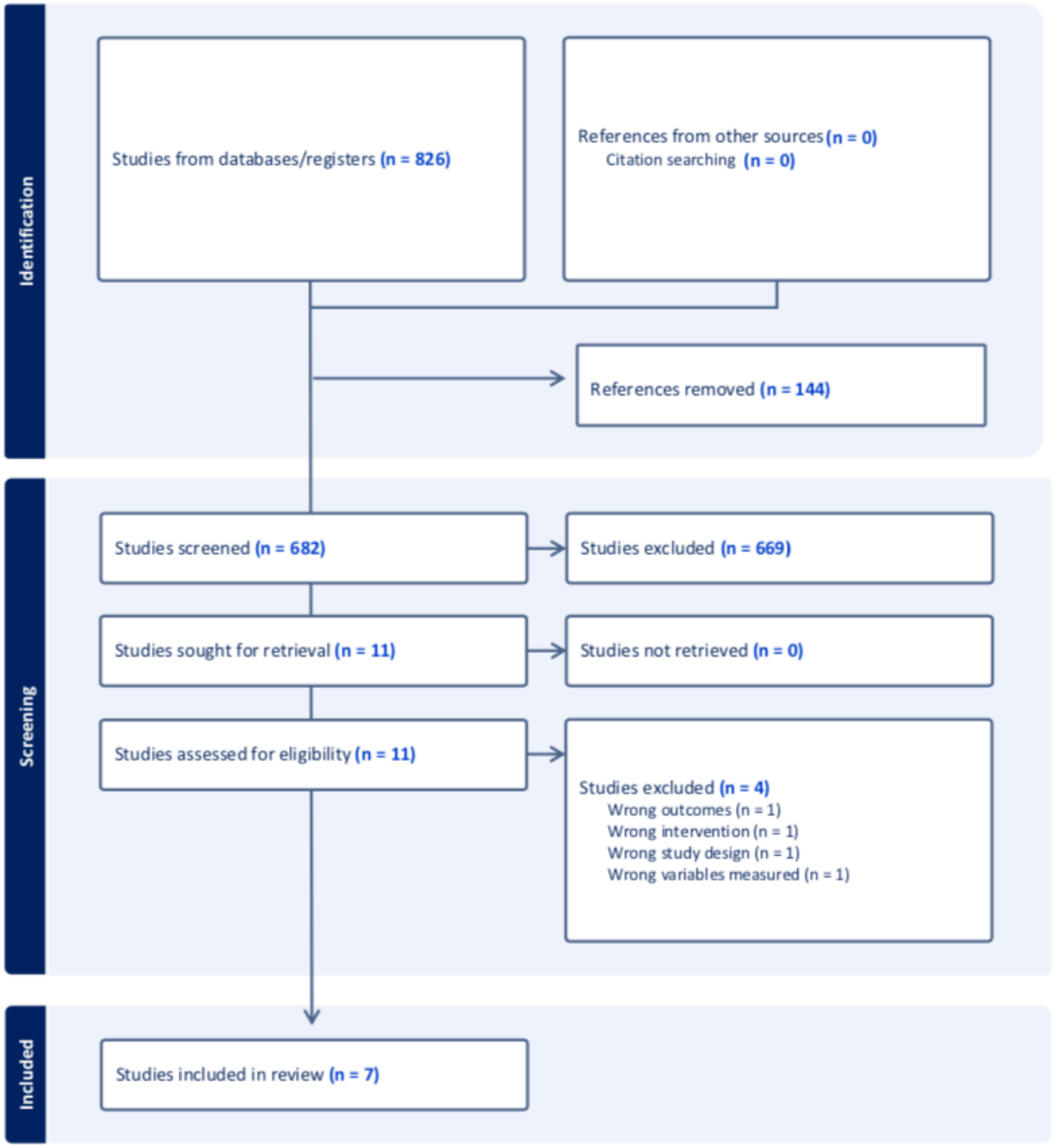
Discrimination
Social capital
Racism/Race
Stigma
Social support/cohesion
Structural conflict
Crime
Violence
War
Health services
Health access
Health affordability
Quality of health services
Insurance
Hospital*
Healthcare*
Gender
Biopsychosocial literature
Stress
Trauma
Allostatic load
Risk conditions
Infrastructure
Social services
Poverty
Social disorder
Psychosocial/mental health
Occupation
Capital (social, economic, human, cultural)
Exercise**
Physical activity**
Obesity**
Overweight**
Abdominal liposity**
Wellbeing**

**Indicates keywords excluded from the search to increase sensitivity.*
***Indicates keywords included in the search but excluded from later stages of analysis.*

Figure 1. Sample search strategy.

SLE or lupus AND social or income or finances or financial need or financial status or socioeconomic status or economic status or education or employment or job security or working life conditions or work or job or career or food security or food insecurity or nutrition or diet or housing or house or dwelling or home or neighbourhood or early life or discrimination or racism or stigma or gender or conflict or violence or crime or health services or health access or health affordability or insurance or stress or trauma or allostatic load or poverty or psychosocial or mental health or occupation or exercise or physical activity or obesity or overweight or wellbeing AND cardiovascular disease* or coronary or angina or infarction or transient ischaemic attack or TIA or ischaemic stroke or ischaemic heart disease or cerebrovascular event* or cerebrovascular accident* or stroke or heart failure or peripheral artery disease or peripheral vascular disease or ST elevation or occlusion or stenosis or claudication

Figure 2. PRISMA flow chart of the study selection process.



Author(s), Year	Themes Explored	Study objective	Study population	Methodology	Key findings
Pons-Estel et al., 2009	Socioeconomic status; Education; Race; Gender; Other: Marital status	To determine the features predictive of atherosclerotic damage in patients with SLE (using SLICC damage index: cardiovascular domain)	LUMINA (Lupus in MInorities, NAture vs nurture) cohort comprised of 637 Hispanic, African-American and Caucasian patients who meet at least 4 ACR criteria for SLE, are >16 years, and have disease duration <5 years.	Longitudinal – logistic regression	Male gender was associated with CV damage in univariate and multivariate analyses. Years of education was negatively associated with CV damage.
Scalzi et al., 2010	Race/Ethnicity	To determine whether racial disparities exist with regard to the age at which patients with SLE experience CVD and CVD-associated death	Clinical records for all adult patients >18 years identified as having SLE by ICD-9 classification were obtained from the Nationwide Inpatient Sample (NIS) database.	Cross-sectional – logistic regression	Black women with SLE were the youngest to experience CVD, while white patients were significantly younger than racialized groups. Black patients were 9.6 years younger than white patients at the time of first CVD hospitalization. Black women were the youngest to have in-hospital CVD-associated death and had a

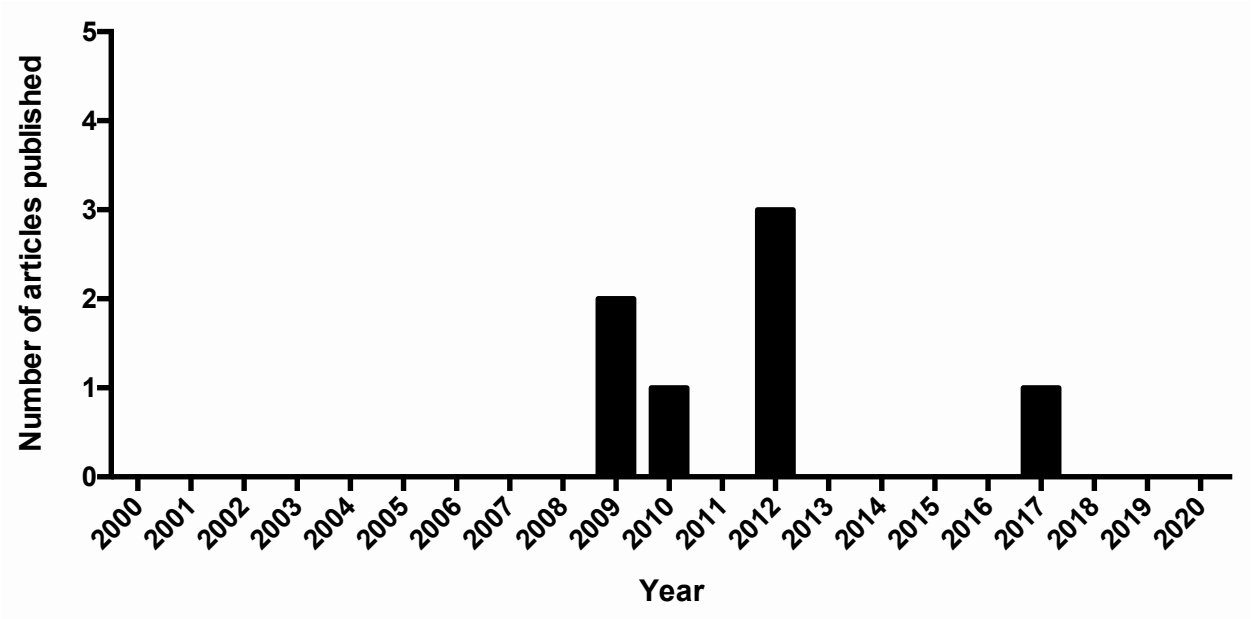
					consistent decline in mortality with age.
Maynard et al., 2012	Socioeconomic status; Education; Race	To investigate whether education or income levels are associated with cardiovascular risk factors and outcomes in SLE	1752 patients from the Hopkins Lupus Cohort with SLE as diagnosed by the principal investigator who were either white or African American.	Longitudinal – logistic regression	Both income and education were associated with cardiovascular risk factors and outcomes, but these relationships differed for African American and white groups.
Rhew et al., 2009	Socioeconomic status; Education; Race	To compare traditional and SLE related risk factors for CVD, and to compare the various measures of subclinical CVD in African American and Caucasian women with SLE	309 women from the Chicago Lupus Database and Pittsburgh Lupus Registry who met at least 4 ACR criteria for SLE, were >18 years, and had no history of CVD events. Only African American and Caucasian patients included.	Cross-sectional – logistic regression	African American women with SLE are twice as likely to have carotid plaque, and more frequently exhibited traditional risk factors for CVD than Caucasian women with SLE.
Tan et al., 2012	Race/Ethnicity; Gender	To compare key clinical characteristics of SLE among male and female patients in a multiethnic population	1979 patients with SLE from the Hopkins Lupus Cohort who were white or African American.	Cross-sectional - comparative	African American men with SLE were more likely than white men with SLE to have CV damage and hypertension.

Jorge et al., 2017	Race; Mental health	To evaluate the relationship between depression and progression of subclinical atherosclerosis in women with SLE	149 women with SLE from the SOLVABLE cohort who met at least 4 ACR criteria for SLE and were >18 years. 126 healthy controls were matched by age, ethnicity and zip code.	Longitudinal – logistic and linear regression, multivariate analyses	Patients with SLE had significantly higher depression at baseline than those without. Baseline depression was associated with increased progression of carotid intima-media thickness (CIMT), but not carotid plaque, in the SLE group, and this was independent of traditional risk factors.
Greco et al., 2012	Education; Mental health	To evaluate the association between depression and vascular disease in SLE	161 women with SLE from the Pittsburgh Lupus Registry that met at least 4 ACR criteria for SLE, were >18 years, and had no history of CVD	Cross-sectional – logistic regression	Years of education was associated with vascular disease. Depression was more prevalent among women with SLE who had vascular disease, compared to those without. Patients with depression had nearly 4-fold increased odds of developing vascular disease independent

	of traditional risk factors.

Table 2. Summary of findings from selected studies.

Figure 3. *Trends in publication of selected studies over time.*



CHAPTER FIVE

Manuscript #3: "Information is power": A qualitative exploration of co-producing education resources about cardiovascular disease in partnership with the systemic lupus erythematosus (SLE) community

E. Shantz, S.J. Elliott, C. Sperling & M. Y. Choi

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition affecting 1 in 2000 Canadians (Fatoye et al., 2018). In SLE, one's own immune cells and autoantibodies attack normally healthy organs and tissues, resulting in symptoms such as extreme fatigue, muscle and joint pain, kidney issues, and skin rash, including a characteristic butterfly-shaped rash on the face (Lupus Research Alliance, 2023). In addition to these physical impacts, people living with SLE also experience psychosocial impacts (e.g. worry, fear, anxiety) (Sutanto et al., 2013b), mental health impacts (e.g. depression, cognitive issues) (Jolly, 2005; Meszaros, Perl, & Faraone, 2012a), and financial impacts (e.g. cost of treatments, time lost from work) (Dixon et al., 2022), among others, due to their illness.

SLE also exhibits striking social disparities; 90% of patients are women (Izmirly et al., 2021), and racialized populations such as Black, Indigenous, Hispanic and Asian groups are significantly overrepresented (Barnabe et al., 2012; Ferucci et al., 2014; Lim et al., 2014). These groups also experience worse health outcomes than their white counterparts (Merola et al., 2014; Somers et al., 2014). Low socioeconomic status and having fewer years of education have

consistently been associated with increased disease damage and poorer overall survival (George et al., 2017; McCormick et al., 2020).

While medical interventions for SLE have patients living longer, co-morbidities with other infectious and chronic conditions have become an increasing concern (Arnaud & Tektonidou, 2020). Indeed, one of the primary drivers of SLE-related morbidity and mortality is cardiovascular disease (CVD) (Barber et al., 2021). Evidence indicates that patients with SLE are more than twice as likely to experience cardiac events such as myocardial infarction and stroke (Antonio et al., 2017). While traditional risk factors such as age, smoking and obesity have been shown to be important in the development of CVD for individuals with SLE, this population also faces additional risks due to ongoing inflammation, immune dysregulation, and prolonged treatment with corticosteroids (Lu et al., 2021). SLE disease activity and associated tissue damage has also been strongly implicated in atherosclerotic processes (Frostegård, 2023).

While there have been calls for improved screening and detection practices among this group, current risk prediction models do not account for SLE-specific factors, and thus perform poorly in this context (Sivakumaran et al., 2021). Moreover, much of the CVD literature to date has focused primarily on men (Dougherty, 2011; Jin et al., 2020), while the majority of patients with SLE are women. Emerging research demonstrates that CVD manifests much differently in women, presenting with different symptoms, and some female-specific risk factor related to hormonal conditions and pregnancy are left unaccounted for (Geraghty et al., 2021; O'Kelly et al., 2022). Though women are more likely to adopt preventative behaviours, they less frequently receive healthcare follow-up, cardiac investigation and treatment (Walli-Attaei et al., 2020). Recognizing these inequities, the American Heart Association issued a global call to action to

reduce the risks and burden of CVD in women through collective education, advocacy, optimized clinical care and community engagement (Wenger et al., 2022).

Given the existing social disparities in SLE epidemiology and outcomes, the additional risks of CVD function synergistically to position this already high-risk population as particularly vulnerable. To this end, our research team sought to co-develop a patient education resource designed specifically for the SLE community using an integrated knowledge translation (iKT) approach. The aims of this resource were to increase knowledge and awareness around the risks of CVD for patients with SLE, and to promote empowerment and behaviour change around prevention and management strategies. In line with iKT approaches to research, we sought input and feedback from knowledge users at all stages of the research process to ensure that the research deliverables were useful, useable and meaningful (Dixon et al., 2023; Graham, McCutcheon, & Kothari, 2019). The specific objective of this study was to obtain knowledge user feedback on the patient education resource and the potential for a novel risk monitoring tool, with the ultimate goal of incorporating this feedback into the final version of these deliverables for dissemination.

2. Methods

One focus group (N=5) and in-depth interviews (N=5) were conducted to obtain knowledge user input, feedback and recommendations on the patient education resource and a future risk monitoring tool. This study was approved by the University of Waterloo Office of Research Ethics (ORE#44339).

2.1 Integrated Knowledge Translation (iKT)

In line with our iKT approach, we leveraged an existing transdisciplinary (Elliott, 2011) research team comprised of one clinician-scientist (MYC), one senior researcher (SJE), one doctoral student (ES), a research assistant (KB) and a patient partner (CS) with lived experience with SLE who is trained in research. The research team met virtually on a bi-weekly basis for peer debriefing, to discuss project updates, and review emerging results. All were involved throughout the research process and provided recommendations at key stages.

2.2 Patient Education Resource

To educate patients with SLE about the risks of CVD, the research team collaboratively developed a patient education resource. Based on the existing literature, and anticipated knowledge user needs, an outline for the resource was developed. The literature surrounding SLE and CVD was reviewed and synthesized, and key messages were prioritized for inclusion in the document. Professional graphic design services were contracted to design the document and graphics. The research team reviewed the initial draft and provided feedback. Team recommendations were used to revise the resource prior to the study.

Topics covered in the document include what is CVD, why those with SLE are at higher risk, who within the population is most at risk and prevention/management strategies to reduce risk. The document is written in plain language for a general audience (i.e. eighth grade reading level (Hutchinson et al., 2016) and includes links to additional evidence-based resources for more information.

2.3 Focus group

A focus group-style webinar was held online via Zoom with key informants. Key informants were purposively sampled based on their expertise in either SLE or CVD (e.g. advocacy organizations, physicians, researchers). After initial contact with prospective participants, snowball sampling was implemented to allow key informants to invite additional members of their organizations. Selected key informants were invited by email. Interested participants were provided with a copy of the patient education resource to review before the meeting.

A semi-structured facilitator guide and meeting agenda were developed with open-ended questions and probes to stimulate discussion around four main themes: i) experiences of SLE, ii) knowledge and experiences about CVD in SLE, iii) the lay document and iv) the SLE-CALCULATOR. All materials were reviewed in full by the research team, including our patient partner, who provided input and feedback. The facilitator guide was piloted ahead of the meeting to ensure all questions were understandable and solicited discussion around anticipated topics.

The focus group was 90 minutes in length. The meeting was structured with a 30-minute presentation followed by 60 minutes of discussion. The presentation portion provided an overview of the research team, the purpose and objectives of the research, and the research deliverables to be discussed (i.e. lay document and SLE-CALCULATOR). The discussion portion was facilitated according to the facilitator guide and agenda. During discussion about the lay document, the lay document was able to be viewed by all participants using the screen share feature. All research team members attended the session to observe and add to the discussion where necessary. The meeting was audio and video recorded and transcribed verbatim for qualitative analysis.

2.4 In-depth Interviews

One-on-one, semi-structured in-depth interviews were held online via Zoom with patients with SLE. Interviews were held with patients rather than a focus group as we recognized that our participants may experience intermittent illness that could impact their abilities to fully participate. Interviews provided more flexibility for patients to participate when they felt well, reschedule if they felt unwell, and join remotely (e.g. from home or work). As many patients with SLE prefer not to disclose their illness, interviews also provided privacy and anonymity (Dixon et al., 2022). All patients were adults >18 years of age who had previously received a diagnosis of SLE and were currently receiving treatment or follow-up. Patients were recruited from MC's clinical rheumatology practice in Calgary, Alberta. Interested participants were provided with a copy of the patient education resource to review before the meeting. Protocols and materials used for the focus groups were amended for use in a one-on-one interview setting but were otherwise prepared in the same manner as described above.

Interviews ranged from 28-53 minutes in length. The interview structure was modelled based on the focus group (described above), but compacted, with 15 minutes for presentation and 45 minutes for discussion. Interviews were audio and video recorded and transcribed verbatim for qualitative analysis.

2.5 Qualitative Analysis

Transcripts from the focus group and interviews were analyzed thematically using NVIVO software. Unique codes were assigned to overarching themes and sub-themes to collect relevant sections of text corresponding to each theme, and to determine their relative frequencies within the transcripts. Codes were developed deductively (e.g. codes determined based on prior

literature searching and possible responses to questions) and inductively (e.g. emerged from the data during analysis). Inductive codes were developed as transcripts were continuously read and reviewed throughout the analysis process. When themes emerged that were not in the codebook, they were added and data was iteratively reviewed for relevant text. Coded sections of text were reviewed within the context of each code to ensure consistent interpretation of the text across transcripts and throughout the analysis process. Qualitative data sources were triangulated during analysis and interpretation to confirm validity and construct a more complete representation of the research findings (Farmer et al., 2006).

3. Results

3.1 Participants

Key informants who participated in the focus groups encapsulated a number of roles, identities and experiences related to SLE and CVD. Of the five participants, three were representatives from SLE advocacy organizations, and one represented a CVD-related advocacy organization. Two were researchers; one in the area of SLE and one in clinical studies. One participant was a physician working in hematology practice. Three key informants were also patients with SLE.

The five patients who participated in interviews described experiences spanning mild, moderate and severe SLE disease. Two self-identified as people of colour, and one patient was also an MD, although they practiced outside the scope of SLE.

3.2 Knowledge and Experiences of CVD

Most of the participants who were living with SLE were knowledgeable about the disease and open about its impacts on their lives. While many recounted the many physical challenges of SLE (5/5 interviews; 3/5 FG), some also relayed impacts related to mental/psychosocial health (3/5 interviews; 1/5 FG), careers and employment (2/5 interviews), and family and relationships (1/5 interviews). Many participants highlighted their experiences in relation to others', emphasizing the high variability in SLE symptoms and severity.

When prompted about their knowledge of CVD, many of the participants who were not health researchers or practitioners were considerably less confident. While roughly half of the interview participants (3/5) identified the heart, lungs and blood vessels as the major organs involved, most spoke to the importance of a healthy lifestyle (4/5) in preventing CVD.

Across both the interview and focus groups, CVD-related conditions were commonly recounted (Table 1). The most frequently mentioned were heart attack and stroke, but there was some confusion about what constitutes CVD outside of these two clinical manifestations. As one participant discussed:

> *"I talked about this with my friend the other day, she has a pacemaker. So, does she have cardiovascular disease? I had stents put in in, a couple years ago, right? So, do I have? But it's better now, I don't have anything. But do you still have cardiovascular disease? That's the question. Kind of like, well, you have the pacemaker because you had cardiovascular disease. And I had a stent put in because I had cardiovascular disease. But it seems to like, cover, like, anything from a stroke to a heart attack to clogged arteries to, you know, a weak heart. It's kind of, like, but if somebody had asked me, you know, maybe six months ago, I would say no, I don't have cardiovascular disease. But I*

do. Right? If I've had stents put in, I'm assuming that I have cardiovascular disease. But it's one of those things, like, it's, like some people have it and are fine, and some people find out about it the hard way, right? So, yeah, that's another kind of, it encompasses a lot." – Participant 2, SLE patient

Indeed, several participants had previous lived experiences with CVD that they related to throughout the discussion. A total of five participants (2/5 interviews; 3/5 FG) had experienced one or more of stroke (N=1), heart attack (N=1), bypass surgery (N=1), deep vein thrombosis (N=1), issues with blood clotting (N=1) or pericarditis (N=1). Notably, all of the participants who had experienced CVD events also had SLE. Similarly, all of the participants with SLE also described themselves as being at high risk for CVD, but this was rarely attributed to SLE (N=1); other reasons for identifying as high risk included a family history of CVD (2 interviews; 1 FG), previous CVD events (2 interviews; 1 FG), or high blood pressure (2 interviews; 2 FG). Despite the knowledge that they were considered high risk, participants had little clarity about what the interaction of multiple risk factors meant for them, and how this impacted their overall health.

"I know I am probably at higher risk than others… However, having said that, I don't know specifically how much of a risk I'm at." – Participant 5, SLE patient

"In my case, I knew I was at higher risk of cardiovascular disease both because of my family history and because of lupus, but I didn't know how much higher risk. Because I was coming across different figures and, something said twofold and you know, you're getting all different information about how much risk is involved." – Participant 6, Key informant

Although nearly all of the participants living with SLE had either identified themselves at high risk for CVD or had had a previous CVD event, only three participants recalled discussing information about CVD risk or prevention with one or more of their physicians. Seven of the participants did not recall discussing this with one or more physicians (some mentioned experiences with more than one physician, e.g. family doctor or rheumatologist). One participant reflected:

> *"I also think the rheumatologists need to keep a closer eye on this and educate their patients. Like, when they're first diagnosed, say okay, because you have lupus you have to be really careful of this, this and this, because you are more likely to have cardiovascular disease. At least mine, there was no prophylactic advice for avoiding a stroke… it's got to start at the very beginnings so that patients know right away the types of things that might happen because of lupus. You know, in addition to the typical lupus symptoms."* – Participant 6, Key informant

Three participants recalled doing their own research on CVD, citing advocacy organizations (e.g. Lupus Canada or Heart & Stroke Foundation) and webpages affiliated with hospitals or clinics (e.g. Johns Hopkins or Mayo Clinic) as primary sources for "reputable" information. Most of the participants who had not independently researched the topic stated that it simply wasn't "top of mind". However, some participants enacted "not knowing" as a coping mechanism to protect their mental and emotional wellbeing:

> *"Sometimes you do want to know what could happen and sometimes you don't want to know what could happen. Right? So, I think if I, if my condition changed or my symptoms were more severe, then maybe I'd look... I know this is a terrible thing to say, but*

sometimes ignorance is bliss. Right? Like if I don't know what's coming then I won't, it's kind of like a double-edged sword. Like, you want to know what can happen, but then you don't want to, every time you get a twinge you don't want to think, oh, that's it." – Participant 2, SLE patient

"I did look up what's the evidence. And the more I read, the less I feel comfortable… I was like, oh my god, I don't know if I should be reading all of these things, if I should just let it go… But every so often I just try to, you know, I try to read up and that just makes things worse, I feel like. I don't know." – Participant 4, SLE patient

3.3 Patient Education Resource

Participants generally responded positively to the patient education resource, and many cited that they believed it filled a knowledge gap for not only patients with SLE, but also physicians and family members. Participants stated that the text was clear and readable, the content was informative and organized, and that they felt the information was helpful and credible. They felt that the graphics were attractive and enhanced reading of the text, and that the length of the document was suitable for providing information while being "digestible" and "not overwhelming". One participant emphasized the importance of knowledge user feedback in ensuring that the resource was useful and meaningful:

"I think it's great you're getting input from other patients. And I think that's important. Because at the end of the day, hopefully they're the ones that are going to be using it."- Participant 5, SLE patient

While participants were overwhelmingly supportive of the resource, they provided a number of suggestions to enhance its impact and usability. Drawing on their own experiences and knowledge gaps, participants identified a number of areas across the document that required additional explanation, or additional topics that should be addressed. For example, key informants widely agreed that more attention should be paid to brain involvement in CVD and outcomes such as stroke throughout the resource:

> *"One thing is that when people talk about cardiovascular disease, medical professionals know that that includes strokes, so the brain is involved. So, some of the diagrams and even the content… doesn't reflect the stroke risk as much… It's the heart, blood vessels, but it also encompasses the brain."* – Participant 6, Key informant

Other recommendations included the introduction of several additional risk factors: stress, sedentary lifestyle, vaping, and cannabis. Focus group participants were in consensus that these were important risk factors in the current Canadian context, particularly for younger groups, who are often removed from conversations around CVD due to perceived lower risk.

In reviewing the resource, participants also provided important insights into how to tailor content towards those with SLE specifically, while also remaining inclusive to the diverse range of abilities and identities represented within the SLE community. A particular focus of this conversation was modifying language around prevention practices to remain inclusive of those experiencing physical symptoms (e.g. fatigue, pain, or varying energy levels). For example, when discussing exercise as a strategy to reduce CVD risk, one participant stated:

"I'm wondering if the image is to show somebody lifting a weight? I think that's important, but should it not be somebody walking for cardiac health? …something that's realistic with lupus patients being able to do." – Participant 7, Key informant

Another added:

"Quite often, lupus patients have some mobility issues and with their joints, so, I mean, a certain amount of weightlifting is good but, like you say, maybe the emphasis should be more on cardiovascular type of activity." – Participant 8, Key informant

Building on the principle of inclusivity, participants also suggested a number of avenues for enhancing accessibility of the resource. One major suggestion was to release the document in different languages –both English and French, at minimum – but participants also identified that the online location of the resource might be a barrier to some:

"I know some people don't have access to the internet but for the most part, people are accessing information online. But even if they could have, like, a sheet of paper to, you know, have available. Or a brochure or something for even the patients... I think there should be two options. It should be in various places where they can access this information. Maybe could even work in conjunction with other organizations… as much as you can get it out there as possible." – Participant 5, SLE patient

Participants were also highly conscious of the emotional impacts of reviewing information about the potential dangers of CVD, both for themselves and for others.

"It's just not fair. People with lupus have a higher risk of like, things, like everything." – Participant 1, SLE patient

One participant highlighted that, because of these difficult emotions, the information presented should be as concise and easy to read as possible:

"Well, if you have the disease and you're looking at this, like, you're probably going to feel a bit emotional. Maybe even overwhelmed. So, it's like, as much as you can spoon-feed, I guess, is, is better." – Participant 3, SLE patient

On the other hand, several participants felt that "knowledge is power", and that while this information might be challenging, it was an important tool in empowering themselves to take action for their own health:

"If you can do anything to help your situation, I think that's important. To have some control. Because I think with lupus, we often feel things are out of our control. So, if this is something that we could maybe do to help prevent potential problems, then I think information is power. If you have the information, it gives you more confidence… in managing your disease." – Participant 5, SLE patient

Indeed, many participants felt they obtained important takeaways from the resource, and that this was important information to share with the SLE community. Three interview patients were candid about having no previous knowledge of the interactions between CVD and SLE. As one patient shared:

"I thought it was interesting… There was information in there I didn't really know about despite having had this for 20 years now… I've had lupus for most of my life and I just haven't come across this, like, CVD, at all. So, I think I can't be the only one." – Participant 3, SLE patient

3.4 Risk Monitoring Tools

Participants who were living with SLE were universally interested in using a tool to calculate and monitor their CVD risk that was developed specific to SLE-related risk factors. Three patients with SLE indicated that they would also be interested in providing their doctor with such a tool.

When prompted about what type of online platform would be preferred for a risk monitoring tool, participants had divided opinions between a website (3 interviews; 2 FG) or a mobile app (1 interview; 3 FG). Reasons that a website was preferred were the convenience of visiting an Internet browser over downloading an app (N=2), that a website would be easier to find (e.g. via Google search) (N=1) and more widely accessible (e.g. those without smartphones) (N=1), that the tool would not be used frequently (N=1), and fear of computer viruses transmitted through apps (N=1). Preferences for an app were due to privacy concerns (N=1), less maintenance required (N=2), the ability to store continuous data (N=1), use apps more often (N=2), and ease of transferring data to a physician (N=1). Across both groups, ensuring both privacy of personal information (N=4) and accessibility to a broad audience (N=6) were significant concerns. Overall, most participants agreed that there were pros and cons to both platforms, and indicated that they would be open to using either or both.

Participants were asked what information or resources should accompany the tool to enhance its usefulness and usability. Most frequently mentioned were including information on prevention and steps to take to reduce risk (4 interviews), a description of how user information would be kept private (1 interview; 3 FG), and explanations of the risk scores (2 interviews). Others requested detailed instructions for use (1 interview), links to other resources (1 interview), and a minimal design (1 interview).

While online tools are frequently used in health, research suggests that they are not always widely trusted (Cardwell et al., 2023; 2022). When asked what features would indicate that an online tool was trustworthy, participants cited an association with a hospital or university (3 interviews; 1 FG), descriptive author information (e.g. who created the tool and what are their qualifications) (N=2 interviews; 1 FG), endorsement by their physician (3 interviews), association with an advocacy group (1 interview), academic references (1 FG); and that there were no advertisements on the platform (1 interview).

Overall, many participants felt that this type of tool was needed by the SLE population and would have significant impact. When prompted to share how knowing this risk score might impact their lifestyle choices, one participant shared:

> *"I think if you see it there and you have some actual tangible numbers that you can look at… like if I was a little bit higher risk, I think you would have an incentive to say, well, there are some things I could do to manage that. I personally think I would use it… I think people do want to improve their health, for the most part. And if they've had some issues, you know, that have been, you know, an unpleasant experience, then I think you strive to do something to prevent that."* – Participant 5, SLE patient

Another participant felt similarly, sharing that knowing their risk score would motivate them to create lifestyle and behaviour changes:

> *"I think, maybe like a little shock and awe. Not shock and awe, but a little like, [gasps]… But with fairness, it might take, like, that's what it may take, right? …Heart disease runs in my family. My dad and my grandpa both had it, you know? Or have it. But, I mean… I don't need anything more to happen, you know?"* – Participant 1, SLE patient

4. Discussion

This study demonstrates that while patients with SLE generally have a high degree of knowledge about SLE, they have limited information about the associated risks of CVD. Even participants who had previously experienced a CVD event were not aware of the relationship between SLE and CVD, though they identified themselves as "high risk" for other reasons. Most did not recall discussing this topic with their doctors, instead relying on independent Internet searches for information or otherwise making an intentional choice not to seek out additional information as a coping mechanism. These findings are in line with similar studies in the United States - as many as 58% of patients with SLE surveyed study had never received CVD related counselling from a physician (Scalzi et al., 2008). Of a subset of patients who self-identified as high risk, only 57% received counselling (Scalzi et al., 2008). Our findings, taken together with the literature, highlight the urgent knowledge and care gaps among this population, and join previous calls for improved risk monitoring and patient education (Costenbader et al., 2004).

Therapeutic patient education (TPE), or the use of non-pharmacological educational initiatives to manage disease, has previously been successful across a number of contexts related to CVD (Labrunée et al., 2012). To this end, we sought to co-produce an educational resource

along with knowledge users. The variety of knowledge users who participated in this study provided critical input; while the resource was generally received positively, and participants felt it was useful in raising awareness and promotion actionable prevention and management strategies, they offered recommendations for a number of areas where additional explanation was needed and/or additional topics should be addressed. In particular, knowledge users made significant contributions in making the content accessible and inclusive. In addition to voicing their own needs related to the resource, participants recognized and advocated for the SLE community as a diverse group with a range of disease impacts, (dis)abilities, interest levels, personal histories and experiences, identities, and healthcare access, and ensured that all aspects of the documents were as inclusive as possible. For example, participants recommended that advice for physical activity should include ways to exercise for those with lower energy or mobility levels (e.g. yoga or stretching), and be sensitive to the episodic nature of SLE symptoms (e.g. "listen to your body").

In addition to the content, participants also identified novel audiences for the resource. While this was primarily intended by the research team to be for patients themselves, participants were enthusiastic about sharing this information with their families, caregivers, and even their physicians, both to foster understanding about CVD, but also to raise awareness about SLE more broadly.

Knowledge users were unanimously interested in the idea of a novel risk monitoring tool developed specifically for those with SLE; however, they were equally divided between using an app or website to access such a tool. This result marked a significant shift for the research team, who had previously anticipated that users would prefer an app. Based on this feedback, a tool is currently under development housed by a website, with the potential to develop an app in the

future. Knowledge user ideas about accompanying information and indicators of trustworthiness are also being taken into account during this process to increase uptake and usability.

Overall, these results are in line with findings from other studies leveraging iKT and knowledge user input to make research outputs more useful, useable and meaningful. Through engaging knowledge users, researchers are able to *co-produce* research deliverables specifically tailored to the unique needs of the intended audience. In this process, knowledge sharing is bidirectional; while researchers gain insight from knowledge users, participants were similarly gaining knowledge and learnings through engaging with the resource. Indeed, many remarked that they were going to re-visit the document and some of the associated resources at the end of their session. In general, knowledge users from both groups were enthusiastic about engaging with research and offering their perspectives for the greater good of the community.

A considerable strength of this study is our iKT approach. While we engaged with a number of knowledge users, we also had a patient partner trained in research guiding this process as an equal member of the research team. Our qualitative approach also engendered feedback from a number of different knowledge user types, providing a number of perspectives. While key informants understood the Canadian SLE community broadly, patients were able to give specific feedback based on their unique experiences. We were also able to include physicians, who had medical expertise on the topic, and researchers who were experts in SLE to ensure that all information was evidence-informed and accurately presented.

We recognize some limitations to our approach. Due to logistical constraints, we had a limited number of participants. Moreover, all of our patient participants were from the same geographical region, and therefore may not represent healthcare experiences from other Canadian contexts with differentially operating healthcare systems. Though we sought maximum

variation from within the participant pool, we had limited representation of participants who self-identified as Indigenous or other racialized groups. Given that these populations face particular risk of both SLE and CVD, specific input from these individuals would have been particularly valuable. However, this is in line with issues in SLE research more broadly, where minority groups are less likely to participate in research (Falasinnu et al., 2018; Lima et al., 2020; Sheikh et al., 2019).

5. Conclusions

Overall, this study has demonstrated how iKT approaches can be leveraged to co-produce effective and meaningful patient education resources in SLE. Through engaging a variety of knowledge users with a range of SLE and CVD experiences, this process helped to shape the content, inclusiveness and accessibility of the resource to best meet the needs of the target audience. Knowledge users also advised on best practices for dissemination of the resource through multiple modalities, and identified a number of alternative populations who could benefit from the document's messaging.

In tandem, our discussions with knowledge users demonstrated a critical need for educational resources in this space. While patients with SLE are at significantly high risk of CVD, many lacked specific knowledge about this risk; we anticipate that this resource will begin to fill that gap. However, it is clear that enhanced education and awareness around the risks of CVD in SLE are required not only for patients, but for physicians and other healthcare professionals to reduce morbidity and mortality for this vulnerable group.

Following revision of the document based on knowledge user feedback, this resource will be publicly available online and in print. Future research should evaluate the effectiveness of this

and other TPE resources in improving knowledge and effecting health-related behaviour change, as well as determine best practices for mobilizing patient education to reduce systemic health inequities.

CHAPTER SIX

DISCUSSION

6.1 Introduction

The goal of this research was to explore the biopsychosocial landscape of systemic lupus erythematosus (SLE). To this end, a mixed-methods approach was employed to meet three specific research objectives:

1) To assess theoretical and methodological support for social epigenetics studies of SLE;
2) To systematically investigate the existing literature around the known social factors influencing the development of cardiovascular disease (CVD) among people with SLE;
3) To engage knowledge users in the co-production of knowledge translation tools to educate patients with SLE about the risks of CVD.

This chapter first presents a summary of the key findings contextualized by current health geographical, social epigenetics, and chronic disease literature. Next, this chapter identifies the theoretical, methodological and substantive contributions of this work. In conclusion, this chapter addresses the limitations of this research, implications for policy and practice, and avenues for future research.

6.2 Summary of key findings

The research findings herein are presented in three manuscripts (Chapters 3-5). This section summarizes important key findings from each of these papers.

Chapter 3 explores the emerging field of social epigenetics using a health geographical lens. The purpose of this paper was to determine whether social epigenetics constitutes a truly novel line of inquiry, and assesses the theoretical and methodological support for such studies in

the context of complex chronic diseases. In so doing, this paper argues that while social epigenetics draws upon existing concepts in the literature, such as the social determinants of health and bio(psycho)social theory, it indeed represents a novel way of viewing – and measuring – environment-health interactions. Furthermore, social epigenetics represents a field that is truly transdisciplinary in its need to include both biological and social scientists, as well as key knowledge users. Looking forward to the practical undertaking of social epigenetic studies, ecosocial theory and lifecourse approaches provide some theoretical support; however, these theoretical underpinnings do not fully represent the dynamic nature of epigenetic processes and greater attention to intersectionality is needed. With respect to methodologies, epigenome-wide association studies (EWAS) and exposomic approaches have been most widely proposed for social epigenetic studies. However, further study is needed as both of these methodologies require significant capital investment and remain in their infancy. We also advocate for the consideration of qualitative and mixed methods approaches to add to this methodological toolbox. In sum, this paper concludes that social epigenetics is more than "old wine in new bottles". To advance this emerging field, we argue that there is a unique role for health geographers in particular to contribute to theory generation, new issues of space, place, scale and time, and unexplored avenues to investigate the relationships between health and place at novel scales.

Chapter 4 takes a substantive approach to investigating social epigenetics through undertaking a knowledge synthesis. In this study, a scoping review methodology was employed to investigate the social factors influencing the risk of cardiovascular disease (CVD) in systemic lupus erythematosus (SLE). Using a scoping review protocol developed to encompass three main concepts – SLE, CVD, and social factors – four databases were searched. 682 studies were

identified, and after a two-phase screening process, seven met the criteria for inclusion in the analysis. All seven studies were conducted in the US between 2009-2017. Four studies were cross-sectional in design, and three were longitudinal. Most employed SLE cohort populations, while one drew from a national-level insurance database. The existing literature centered around four main themes: SES/education, race/ethnicity, mental health, and gender. The groups at highest risk for CVD events were those with low SES/education, Black and other racialized groups, those with depression, and men (relative to women). While these findings provide important points for healthcare and patient education, some gaps in the literature were identified. Future research should endeavour to integrate social theory, advance conceptualizations of race/ethnicity, gender, and intersectionality, expand investigations of mental health to include other conditions experienced by those with SLE, and explore novel geographical contexts, particularly in the global South. In healthcare policy and practice, the identified social factors in this review should be more robustly considered in risk assessment, preventative care and treatment for SLE populations. In addition, patient education resources should be specifically targeted for these groups.

Chapter 5 builds on the findings and recommendations from Chapter 4 to develop a patient education resource for patients with SLE in collaboration with knowledge users using an integrated knowledge translation (iKT) approach. In this study, an educational resource describing the risks and management of CVD in SLE was developed and shared with patients with SLE and advocacy organizations through a focus group and one-on-one semi-structured in-depth interviews. Participants were encouraged to draw on their own knowledge and experiences to provide feedback, comments, and recommendations on the resource. While participants had high levels of knowledge about SLE, many were less informed about CVD. When prompted

about their knowledge of CVD, CVD-related conditions such as heart attack and stroke were frequently recounted, and many participants themselves had experienced such conditions or related procedures. Interestingly, many of the participants currently living with SLE identified themselves as high risk for CVD, but this was often attributed to other reasons such as family history or previous CVD events. Few participants recalled discussing information about CVD in relation to SLE with their physicians, and some had filled this gap by conducting independent online research on the topic. Participants generally responded positively to the patient education resource and many believed it filled an important gap for not only themselves, but also for physicians and family members; audiences that were previously not targeted by the research team. Participants provided a number of suggestions to enhance the resource's impact and usability; for example, advocating for information on additional risk factors (e.g. stress, vaping, cannabis); promoting inclusivity (e.g. modifying language around suggestions for physical activity); and enhancing accessibility (e.g. translation into additional languages, distributing paper copies). Participants were similarly enthusiastic about the prospect of a novel risk assessment tool they could access to measure their risk, and advised on use of website to house the tool as well as resources and information that should accompany such a tool. Overall, patients voiced a critical need for education resources in this space and provided feedback to significantly impact the resource's development and dissemination, rendering the resource more useful, useable and meaningful. In sum, this study demonstrated how iKT can be leveraged to co-produce effective and meaningful patient education resources.

6.3 Contributions

The studies presented in this dissertation make several theoretical, methodological, and substantive contributions to the fields of health geography, and the study of chronic disease and illness more broadly.

6.3.1 Theoretical contributions

The presented work makes four distinct contributions to the associated theoretical literature. First, this research explored and assessed the theoretical support for social epigenetics studies. As a field of study primarily stemming from the biological sciences, social epigenetics has largely remained "atheoretical" with respect to social theory. In Chapter 3, I argue that the integration of social theory is necessary to conduct social epigenetics studies that provide accurate, useful and meaningful results. Subsequently, I critically analyzed the existing theoretical support for such research. In critically exploring the potential for ecosocial theory, biopsychosocial theory, lifecouse approaches, and exposome approaches, among others, to provide a suitable theoretical foundation for social epigenetics inquiry, I determined that there was some theoretical support, but also noted specific gaps. To my knowledge, this was the first exploration – and advocacy for – integrating social theory into social epigenetics research. Further, this study identified a number of opportunities for biological and social scientists to engage in truly transdisciplinary theory generation.

As described in Chapter 2, this dissertation drew on ecosocial theory to frame the research design. Informed by the explorations of the theoretical underpinnings of social epigenetics in Chapter 3, I recognized a particular limitation of ecosocial theory in its capacity for intersectional perspectives. While ecosocial theory provides consideration for a number of

social determinants and associated identities, for example inequalities related to race, income and gender, these are treated as discrete categories. This lies in opposition to feminist perspectives, which view such identities as inextricably linked, and informing one another. As gender was a focus of this work, I drew upon these pinnacles of feminist theory to complement the ecosocial approach with intersectional perspectives. This integration of intersectionality into ecosocial theory contributes an improved lens for the study of complex chronic diseases exhibiting gender disparities and other social inequities in their development, experiences and health trajectories.

This work also drew upon bio(psycho)social theory, which was similarly complemented with feminist conceptualizations of intersectionality. While biopsychosocial theory does implicitly account for gender and other social factors in its explanatory capacity, it lacks explicit attention to intersectionality. In conceptualizing SLE, in particular, as a biopsychosocial condition, existing health disparities with respect to race, gender, income, education, etc., make the intersectional nature of these determinants apparent (Kinsey et al., 2018). To adequately account for this, I expanded traditional perspectives of bio(psycho)social theory to include a more overt focus on the intersection of identities in illness experiences.

A major theoretical contribution, and strength of this work, is its bridging of biological and social science to produce more holistic views of chronic disease, and SLE in particular. Though chronic diseases and illness indisputably encompass both biological systems and social experiences, these lines of inquiry often remain in disparate "silos" of research, and are rarely integrated in a meaningful way. In doing this work, I intentionally draw upon both the biological pathways to disease and the social systems influencing them to construct a holistic picture of SLE. On a theoretical level, this is challenging, as both biological and social sciences exist within their own paradigms; even the word "theory" means vastly different things among these

two disciplines. By drawing upon a range of interdisciplinary theoretical underpinnings (e.g. ecosocial theory and biopsychosocial theory), the foundations of biology (e.g. epigenetics), and social systems (e.g. social determinants of health), I create a view of SLE – and chronic diseases more broadly – that is transdisciplinary (Elliott, 2011). Moving forward, I encourage other scholars to join in this space, bridging together the many aspects of health-related study to piece together more dimensional views of bodies, disease, illness and health.

6.3.2 Methodological contributions

This research employed a mixed methods approach to exploring chronic disease, accompanied by integrated knowledge translation (iKT). This research design and the subsequent findings make five methodological contributions to the broader field.

In Chapter 3, I assessed the methodological potential for conducting social epigenetics studies, as well as their predictive validity. In this study, I identified a number of methodologies that have been previously proposed for social epigenetics, including epigenome-wide association studies (EWAS) and exposome approaches. Deriving from the basic sciences, all of the methodologies that had been proposed or employed in the literature were positivist and quantitative in nature. Noting this gap, and the complexity of the social components of these studies, I proposed the integration of qualitative research in this area. By introducing these methods, which are well-established in social research but novel to this and other biological areas of study, I expanded the methodological landscape to allow for future mixed methods investigations.

In undertaking this research in tandem with an iKT approach, I add to the existing literature on the methodology of iKT. While iKT approaches have increased in the past decade,

particularly in health-related research, there has been a dearth of research on how to *do* iKT, and moreover, how to do iKT *well* (Kothari, McCutcheon, & Graham, 2017; Kothari & Wathen, 2017). Indeed, previous studies indicate that one of the most significant barriers to conducting iKT for researchers is a lack of methodological and practical knowledge (Dixon & Elliott, 2019; Dixon, Shantz & Elliott, 2023). Employing an iKT approach involves much more than simply having conversations with knowledge users – while there is little consensus in the literature on process, it is widely agreed that best practices for iKT include establishing long-term relationships, having regular touch points for knowledge sharing and feedback, and integrating knowledge user perspectives throughout the research journey (Dixon, Elliott, & Clarke, 2016; Lawrence, Bishop, & Curran, 2019; Rishworth et al., 2016). Through explicitly describing and sharing our iKT process, I set out a foundation for other researchers to build upon in their own contexts and with their own transdisciplinary teams.

Stemming from our iKT approach, I contribute to the literature on patient engagement and involvement in specific research processes. In Chapter 4, I detailed a scoping review of the literature conducted in partnership with our patient partner, who has lived experience with SLE. While there is an increasing amount of literature on engaging patient partners (Banner et al., 2019; Bombak & Hanson, 2017; Duffett, 2017), as well as rich scholarship on best practices for scoping reviews (Peters et al., 2022; Tricco et al., 2018), only recently has research begun to describe how knowledge users can contribute to these types of research processes (Pollock et al., 2022). Having a patient partner advise on all stages - from developing search strategy terms to screening papers and interpreting findings – both shaped the review process and assisting in meaning making of the results. By detailing our processes as well as the positive outcomes, I

contribute a blueprint to the literature for integrating patient partners and other knowledge users in concrete research processes that have traditionally excluded non-academic voices.

In Chapter 5, I similarly add to the patient engagement literature by describing how knowledge user perspectives can be leveraged to create health education resources. While the knowledge users in this context were research participants rather than involved as iKT team members, the experiences, suggestions and recommendations they shared were critical to tailoring our education resources for the target audience. Our participants advised on all aspects of the resource from content and language to design and dissemination, and raised significant points for accessibility and inclusivity in particular. In drawing upon their own lived experience as well as their knowledge of the SLE community, the engagement of knowledge users in the development process significantly shaped our research deliverables, outputs and outcomes. By detailing these processes as well as their impact, I encourage other researchers to similarly enact the co-production of resources with knowledge users to maximize usefulness, usability and meaning.

By engaging patients in the research processes, I also contribute to the literature on conducting research with and for individuals who are chronically ill. Due to the episodic and often unpredictable nature of SLE, we recognized that our participants may experience intermittent illness that could impact their abilities to fully participate in the research process. As a result, we decided to make a methodological shift from focus groups to individual interviews. While this did limit interaction between participants, it more importantly promoted equity, inclusion and accessibility by providing more flexible scheduling and meeting times and opportunities for breaks (Morse, 2002). The virtual format also allowed participants to join from any location, with minimal exertion, and without cost. As many patients with SLE prefer not to

disclose their diagnosis due to stigma (Dixon et al., 2022), this format also provided privacy and an opportunity for anonymity. As a result of these flexible practices, I was able to reach participants who were both at work in between meetings, or at home caring for small children, who may otherwise not have been able to participate.

6.3.3 Substantive contributions

The studies herein (Chapters 3-5) make several substantive contributions to the study of SLE, and the chronic disease literature more broadly. Firstly, this work cements social epigenetics as a novel line of inquiry. Given its roots in epigenetics as well as the social determinants of health, scholars have questioned whether social epigenetics is, indeed, a novel area for research, or whether it is simply "old wine in new bottles". By asserting its movement from static to more dynamic models of bodies, new issues of space and scale beneath the body, and its inherent transdisciplinarity, I argue that social epigenetics provides novel insights not obtainable or replicable by other means. Further, social epigenetics marks a measurable, quantifiable and possibly heritable means for place-based health impacts. Thus, I substantively establish social epigenetics as a ripe area for future research, particularly for health geographers.

The scoping review detailed in Chapter 4 provides a knowledge synthesis of the social factors influencing CVD in SLE. Our findings revealed that low socioeconomic status, low education, Black race, depression, and male gender were all important indicators of CVD risk and future CVD outcomes. Importantly, these "risk enhancers" are further compounded by similar risk factors in the general population, as well as social disparities in SLE epidemiology. These results therefore place these already vulnerable groups as at particular risk for CVD complications. To our knowledge, this is the first knowledge synthesis undertaken on this topic.

These findings provide a substantive basis for CVD prevention and risk monitoring in SLE healthcare policy and practice, and outline future opportunities to investigate how other unexplored social determinants of health may impact this process.

Through engaging patients and advocacy representatives (see Chapter 5), I add to the literature on knowledge, attitudes and practices related to CVD in SLE. While this has been explored in one previous US study (Scalzi et al., 2008), it has not been investigated in a Canadian context, or in recent years (e.g. since the rise of social media). Our findings indicate that while those living with SLE have a high knowledge of SLE, they are less informed about the associated risks of CVD. Indeed, many of our participants did not recall discussing CVD risk or prevention with their healthcare providers unless it was related to a CVD events. While many were interested in learning about CVD and preventative measures, they did not have access to evidence-informed resources. These findings contribute to an existing body of knowledge on SLE experiences and outline a critical need for patient education in the CVD space.

Taken together, the studies detailed in Chapters 3 and 4 make important contributions to the CVD risk landscape in the context of SLE. While the scoping review identified a number of social factors associated with increased CVD risk, focus groups and interviews with patients indicated that general knowledge about CVD was largely low, with the exception of participants in medical professions. Taking an intersectional lens, we can see how these factors function synergistically to create sub-populations at particular risk. For example, those with low general education or those with depression, both of which were identified as being at high risk of CVD, would likely face barriers in seeking out and/or accessing medical information; this may be further compounded by other risk factors such as race, sex/gender, socioeconomic status, etc.

These findings underscore the essential need for accessible and inclusive patient education, as well as the need for additional work with an intersectional focus.

The research in this dissertation positions SLE as a condition which is both biopsychosocial, and place-based. This builds upon burgeoning calls for SLE and other complex chronic disease to be viewed – and studied – as conditions that are biopsychosocial in development, etiology, and experience (Kinsey et al., 2018). Our exploration of the social factors influencing CVD demonstrate the importance of social context; as social systems vary geographically, this context is necessarily place-based. While much geographic inquiry in the study of SLE has been limited to spatial analyses and healthcare accessibility, this work indicates that there is much opportunity to continue to untangle the biological-social interplay in the context of place.

This work also builds upon the literature concerning feminist geographies and geographies of chronic disease. With a particular focus on gender and intersecting identities and circumstances, our findings touch upon many of the themes of feminist geographical inquiry, including corporeality and the body, negotiating illness identities, and interactions with space and place in daily life. While social epigenetics represent a novel scale for the embodiment of context, our substantive investigations reveal the importance of place-based context and lived experience in constructing health trajectories, here investigated as CVD risk. Our qualitative work further reveals some of the coping mechanisms employed by those living with SLE and how these are deeply individual and informed by experience; for example, our participants who coped by seeking out information about SLE and CVD versus those who purposely avoided such information to avoid distress.

This research finally contributes to the emerging field of iKT. As discussed previously in this chapter, while iKT approaches are being increasingly undertaken, there is little consensus on methodology, and their purported usefulness in some contexts have been contested (Crosschild et al., 2021; Kothari & Wathen, 2013; Reimer-Kirkham et al., 2009). The iKT approach undertaken in this research instrumentally shaped the research questions, methodologies, interpretation of findings and dissemination of results. Drawing upon the lived experiences and voices of our patient partner and research participants, our research outputs were rendered more useful, useable and meaningful for the SLE community. Our substantive investigations of this process, and the benefits redeemed, contribute to growing calls for patient engagement and the integration of knowledge users in health-related research with the ultimate goal of closing knowledge to action gaps.

6.4 Limitations

There are some limitations to this research design. For the scoping review, texts were searched in English only due to the language proficiencies of the team. I recognize that additional studies, in other geographic contexts, may have been published in other languages. Furthermore, we collected studies published between the year 2000 and July 2022, when the study was conducted. Any articles published outside of this time frame were not collected. The decision was also made to exclude studies of pediatric SLE, as these conditions exhibit different etiologies (Chung et al., 2007; Mina & Brunner, 2010; Pons-Estel et al., 2017); therefore, these patients were not represented in the dataset. Although every effort was made to ensure the robustness of our search strategy, some relevant articles may not have been captures due to the keywords and/or filters use, and may therefore not be represented in this analysis.

In the qualitative work, logistical constraints limited the number of participants. While we had representation from advocacy organizations and other stakeholders located nationwide, not every active advocacy organization chose to participate in this research study. Our patient participants were all recruited from a single clinic location, and therefore represented similar geographical regions. As a result, their experiences may not represent those from other Canadian contexts with differentially operating healthcare systems. Though we sought maximum variation from within the participant pool, we had limited representation of participants who self-identified as Indigenous or other racialized groups. Given that these populations face particular risk of both SLE and CVD, specific input from these individuals would have been particularly valuable. However, this is in line with issues in SLE research more broadly, where minority groups are less likely to participate in research (Falasinnu et al., 2018; Lima et al., 2020; Sheikh et al., 2019).

While this body of work begins to make connections between social epigenetics, SLE, and CVD, the results do not definitively provide causal mechanisms for this complex interplay. The extrapolation of study findings to the application of molecular social epigenetics studies or healthcare interventions should therefore be done with careful interpretation and in tandem with additional research.

6.5 Implications

This work has several implications for research and healthcare policy and practice related to CVD, SLE, and chronic disease more broadly.

6.5.1 Practical application of social epigenetics research

The theoretical and methodological exploration of social epigenetics detailed in Chapter 3 provides a foundation for the practical undertaking of social epigenetics studies. To adequately align conceptualizations of both epigenetics and social systems, I argue that a transdisciplinary team is necessary for conducting meaningful social epigenetics studies. Within this transdisciplinary team, I advocate for knowledge users to participate and specifically, to advise on ethical issues. Knowledge users may similarly guide the dissemination process, to ensure that scientific results are communicated clearly and in lay language to the general public in order to minimize misinterpretation of the findings.

This manuscript further underscores the need for social epigenetics studies to be theoretically-informed and methodologically sound. While some theoretical and methodological support exists in the literature, further work is needed to address theoretical gaps and more thoughtfully consider the integration of social science ontologies and epistemologies into the research design. In forming this theoretical basis for social epigenetics research, investigators should integrate intersectionality perspectives and consideration of lived experience to produce findings that are not only accurate, but useful in the broader context of health and healthcare.

6.5.2 Risk assessment, prevention, and education for CVD in SLE

The findings in Chapters 3-4 have substantial implications for healthcare policy and practice related to the development and outcomes of CVD in SLE populations. The scoping review revealed several social determinants associated with CVD events and/or CVD risk in those living with SLE, positioning patients who are lower SES, lower education, Black or other racialized groups, diagnosed with depression, and men at particular risk. As such, individuals

belonging to one or more of these groups should be specifically targeted by healthcare professionals for early preventative therapy and regular risk monitoring. When individuals are identified in clinic as high risk, these variables should similarly be taken into consideration during decision-making processes for treatment. In line with the most recent guidelines from the American College of Cardiology, these characteristics should be considered as "risk enhancing factors" in clinical practice (Arps, et al., 2018).

The qualitative findings subsequently revealed that while many patients with SLE had experience with CVD events or associated procedures, and most identified as "high risk" due to family history or other reasons, the majority were unaware that CVD was associated with SLE. Indeed, while patients were well-versed in SLE, they had little knowledge of CVD. Taken together with the knowledge that CVD is one of the most frequent causes of morbidity and mortality in SLE, this highlighted a critical and urgent need for patient education and awareness in this space. Additional studies have identified gaps in other aspects of health-related knowledge for patients with SLE (Hervier et al., 2013; Zirkzee et al., 2014), illustrating a need for tailored evidence-based information and advocacy on a larger scale.

The resources that were co-developed with knowledge users aims to begin to fill this gap, but additional resources are needed. In line with our findings above, particular efforts should be made to reach identified vulnerable groups (e.g. Drenkard et al., 2022; Feldman et al., 2012). To maximize accessibility, educational resources should be free of cost, available in multiple languages and modalities, and distributed from "trusted" points of access. Patients with SLE consistently cite their physicians as their most trusted source of information (Cardwell et al., 2023; Cardwell et al., 2022), yet most participants in our study did not recall ever having discussed CVD risk with any of their doctors. This finding underscores a need to similarly

engage healthcare professionals in CVD education, and encourage more regular touchpoints for risk monitoring and assessment.

6.5.3 Social interventions for SLE

These research findings alternatively provide some substantive support for non-pharmacological interventions for SLE. Drawing on our case study with CVD, as well as studies related to other aspects of SLE, there are increasingly clear connections between spatio-social context and disease etiology (Kinsey et al., 2018). These connections are postulated to be, at least in part, mediated by mechanisms of allostatic load and chronic stress (Sumner et al., 2020; Williams et al., 2014; Yelin et al., 2019). To offset social inequities and associated stressors, social interventions have been proposed as complementary treatments to traditional biomedical models of healthcare (Parodis et al., 2023). Such interventions have been well-studied in the context of lupus, particularly with respect to support groups (Brennan & Creaven, 2016) and online or mobile discussion forums (Dantas et al., 2020; Mazzoni & Cicognani, 2014). These types of interventions serve multiple purposes to enhance patient wellbeing; for example, they not only provide social interaction and support for chronically ill and often isolated individuals, but also facilitate the sharing of knowledge, experiences and coping mechanisms (Mazzoni & Cicognani, 2011).

Recently, social prescription programs have been piloted in Ontario, Canada (Dominik, Nowak & Mulligan, 2021), based on successes across the UK and other regions (Morse et al., 2022). The nature of social prescriptions can range from joining a walking club or yoga class, to attending a knitting circle or arts therapy, or facilitating free-of-cost visits to art galleries, national parks, and other community spaces (Alliance for Healthier Communities, 2023). Though

evaluations of such programs remain in early stages, our findings indicate that those with SLE, and particularly vulnerable groups within SLE populations, may benefit. Such social interventions stand to reduce morbidity and mortality, increase quality of life and promote health equity for the SLE community, as well as those living with chronic disease and illness more broadly.

6.5.4 Towards a patient-informed research agenda

The research herein was conducted in a transdisciplinary team in partnership with knowledge users, and a patient partner with lived experience with SLE. The qualitative explorations further engaged with patients with SLE, advocacy organizations, physicians, and other stakeholders. Our interactions with patients and other partners indisputably shaped the research process, from the inception of research questions to the dissemination of research findings. The focus group and interviews, in particular, not only contributed experiential knowledge and insights, but also identified a number of important gaps in the SLE landscape that should be addressed through future research.

Previous research has shown that patient engagement and iKT approaches lead to research that is more useful, useable and meaningful. Indeed, our iKT approach and research participants not only shaped our research findings, but also enhanced our dissemination process; in addition to dissemination to the academic community through publications and conferences, these results have also been disseminated specifically to the SLE community through a CIHR-sponsored Café Scientifique event. At this event, the research results described herein were presented to a general audience of patients, their caretakers/families, advocacy organizations,

physicians, other healthcare professionals. The presentation was carefully tailored in lay language, and fostered discussion around the research findings and ideas for future research.

I anticipate that such KT activities will lead to more rapid and widespread uptake of the research results in the SLE population as well as for healthcare policy and practice. Recognizing these benefits, and equally the long-term relationships and partnerships built from this process, I advocate for the thoughtful integration of knowledge user perspectives in the SLE research agenda. In so doing, we expect that research guided by knowledge users will be better able to meet patient needs, thereby increasing impact and better promoting health for all.

6.6 Future research

Rich opportunity remains to build on this work with future research. Looking forward to the practical undertaking of social epigenetics work, I have identified rich opportunity for theory generation and methodological innovation in this space. I encourage scholars to begin to integrate more intersectional research approaches in this field, as well as qualitative and mixed methods approaches. Given the historical trajectory of health geography as a discipline (R. Kearns & Moon, 2002) and its current focus on constructing transdisciplinary knowledges and remediating health inequities (Rosenberg, 2014), I postulate that health geographers, in particular, are positioned to contribute to this line of thinking.

Building on the scaffolding I have set out for conducting social epigenetics studies, this work establishes SLE and CVD as opportunities to substantively undertake this work. Given that both SLE and CVD are socially patterned, rooted in place, and linked with specific epigenetic changes (Long et al., 2016; Ordovás & Smith, 2010), investigating possible connections between the "social" and "biological" remains ripe area for future study. Such investigation stands to both

enhance our understanding of social epigenetic pathways and mechanisms, while simultaneously providing insight into the biopsychosocial interplay observed in the course of SLE pathology.

The scoping review conducted herein began to untangle the biopsychosocial pathways in one particular aspect of SLE – the associated high risk of CVD. This review identified several gaps in the literature that future research should address. Building on the existing literature, additional studies into the contributions of social context are required that adopt more nuanced, and less binary, conceptualizations of race and gender (Clayton & Tannenbaum, 2016; Flanagin et al., 2021). Rather than being treated as discrete variables, an intersectional lens should be employed (Holman et al., 2021; Kelly et al., 2021); this remains an opportune area for future theoretical and methodological work. In addition, the link between mental illness and CVD in SLE should be more thoroughly explored outside of self-identified depression; for example, patients with SLE are also at high risk for developing clinical anxiety (Moustafa et al., 2020; Zhang et al., 2017). At this time, a number of social determinants remain unexplored in the context of CVD in SLE; for example, unemployment/job security, food (in)security, housing, structural conflict, and early childhood (Wilkinson & Marmot, 2003). Many of these circumstances similarly trigger chronic stress, a major mediating factor of CVD, and may also impact associated SLE trajectories (Parks et al., 2017; Pawlak et al., 2003). Future studies should endeavour to address these potential impacts. Lastly, our review revealed a significant gap in CVD/SLE studies outside of the United States. As social systems function differently in different places, I recommend further studies explore geographical contexts outside of North America. In particular, there is a dearth of SLE studies in general in the Global South, where the SLE burden is rapidly rising (Carter, Barr, & Clarke, 2016).

I previously described the potential for this work to inform social and educational interventions for the SLE community (see Sections 6.4.2 and 6.4.3). In order to design effective interventions, additional research is needed regarding patient needs, patient interest in such programs, and implementation processes. While our patient education resource endeavours to begin to fill knowledge gaps for patients, the development of additional education programs for healthcare professionals may be synergistically effective in promoting knowledge and awareness. Following the dissemination of our education resource, future research could evaluate its uptake, as well as its effectiveness in increasing knowledge among the target population. Similarly, I intend that future research will evaluate the risk assessment tool in development and its impact on CVD prevention and intervention in the Canadian SLE community.

This work detailed a successful iKT approach and patient engagement practices that instrumentally shaped our research deliverables. Building on these positive impacts, future SLE research should continue to integrate knowledge users to best meet patient needs. More broadly in the chronic disease space, additional stakeholders outside of patients should be considered who equally impact health experiences: physicians and other healthcare professionals, complementary health practitioners, and caretakers, among others. Future studies should continue to advise on best practices for the sustained co-production of health-related knowledge as well as the development of knowledge translation resources to ensure that research is meaningful, useful, and useable, and equally promotes population health and equity.

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APPENDIX A: Scoping review search concepts and key words. The following table lists the three primary concepts and keywords used to develop the search strategy and resulting search string.

LUPUS	SOCIAL FACTORS	CARDIOVASCULAR DISEASE
Lupus SLE Systemic lupus erythematosus	**General terms** Social factors Social determinants Social environment Social conditions Social gradient(s) Social inequities/inequalities **Social determinants of health** Income Social protection Finances Financial need (Socio)economic status Education School* Degree* College/University Unemployment/Non-employment Job (in)security Work/job/career Food (in)security Nutrition** Diet** Housing/House/Dwelling Environment* Neighbourhood Early childhood/life Social inclusion/exclusion Discrimination Social capital Racism/Race Stigma Social support/cohesion	Coronary heart disease Coronary death Coronary insufficiency Coronary artery bypass graft Coronary procedure (e.g. bypass, stent) Percutaneous coronary intervention Angina Cerebral infarction Myocardial infarction Transient ischaemic attack (TIA) Ischaemic stroke Ischaemic heart disease Cerebrovascular events Cerebrovascular accidents Stroke Peripheral artery disease Peripheral vascular disease Heart failure Congestive heart failure ST elevation Non-ST elevation Occlusion and stenosis of carotid artery Claudication

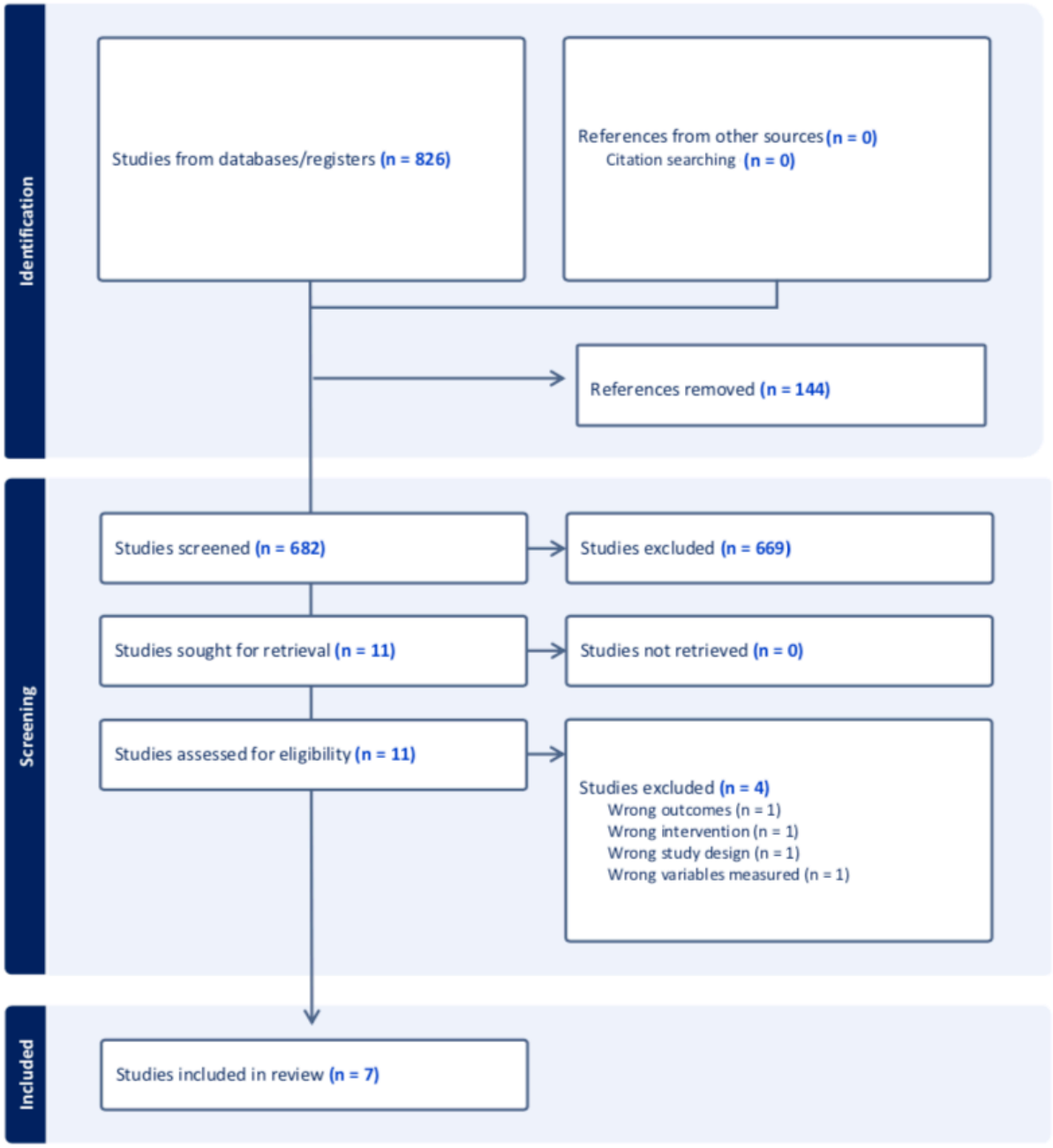
	Structural conflict Crime Violence War Health services Health access Health affordability Quality of health services Insurance Hospital* Healthcare* Gender	
	Biopsychosocial literature	
	Stress Trauma Allostatic load Risk conditions Infrastructure Social services Poverty Social disorder Psychosocial/mental health Occupation Capital (social, economic, human, cultural) Exercise** Physical activity** Obesity** Overweight** Abdominal liposity** Wellbeing**	

**Indicates keywords excluded from the search to increase sensitivity.*
***Indicates keywords included in the search but excluded from later stages of analysis.*

APPENDIX B: Scoping review sample search strategy.

SLE or lupus AND social or income or finances or financial need or financial status or socioeconomic status or economic status or education or employment or job security or working life conditions or work or job or career or food security or food insecurity or nutrition or diet or housing or house or dwelling or home or neighbourhood or early life or discrimination or racism or stigma or gender or conflict or violence or crime or health services or health access or health affordability or insurance or stress or trauma or allostatic load or poverty or psychosocial or mental health or occupation or exercise or physical activity or obesity or overweight or wellbeing AND cardiovascular disease* or coronary or angina or infarction or transient ischaemic attack or TIA or ischaemic stroke or ischaemic heart disease or cerebrovascular event* or cerebrovascular accident* or stroke or heart failure or peripheral artery disease or peripheral vascular disease or ST elevation or occlusion or stenosis or claudication

APPENDIX C: PRISMA flow chart of the study selection process.



APPENDIX D: Semi-structured guides for focus group (key informants) and in-depth interviews (patients).

SEMI-STRUCTURED FOCUS GROUP GUIDE FOR KEY INFORMANTS

INTRODUCTION: Consent

[Facilitator reads:]

Thank you all for joining us today to speak about the SLE-CALCULATOR project. As a knowledge user, your insights are extremely valuable to helping us ensure this research is useful, useable and meaningful for the SLE community. Today, I will be facilitating a discussion on the development of the SLE-CALCULATOR tool and patient education materials describing the risks of cardiovascular disease in SLE.

Please be aware that this webinar will be audio and video recorded. You may choose to keep your camera on or turn it off for the duration of the webinar. No images will be used in any publications resulting from this research, but participating with the video may allow for better communication with the group. Excerpts from the webinar discussion may be included in any publications to come from this research, but any quotations will remain anonymous and your name, title, or any other indication of your identity will not appear. You may withdraw consent or leave the meeting at any time.

I want to remind everyone that there are no right or wrong answers, and we are interested in your honest opinions. We want to ensure that this is a respectful discussion, and that all voices are equally heard. For this reason, the facilitator may, at times, address participants directly. If there are any questions you would prefer not to answer, simply say "pass". We ask that this conversation remains strictly confidential among the present group, however, please be aware that we cannot guarantee this

Before we get started, I ask that you confirm that you have read the information presented in the information letter, that you had the opportunity to ask any questions related to this study, to receive satisfactory answers to those questions, and to receive any additional details that you wanted.

[Participants confirm].

SECTION 1: Overview of the project

- Introductions of research team
- Overview of SLE-CALCULATOR project, research objectives, and deliverables

[Facilitator to pause and ask for any questions before proceeding.]

Theme	Question	Probe

1. Introduction/Background	First, I'd like to have each participant introduce themselves, and I would like to remind you that you may use a pseudonym for confidentiality if you wish. What is your name and your current role?	Do you identify as an SLE patient, advocate or health care professional? What organization do you work for/belong to? What type(s) of activities do you do in your role?
	What does SLE mean to you?	How did you first learn about/become interested in SLE?
SECTION 2: Lay patient education document		
Theme	**Question**	**Probe**
2. Knowledge, Attitudes and Practices	When you hear the term "cardiovascular disease", what comes to mind?	What do you know about cardiovascular disease? What do you not know?
	What knowledge do you have about cardiovascular disease in the context of SLE?	If you have SLE, have you ever discussed this with your doctor? Have you come across this in lupus education before? Or your own searches for health information?
• Present document		
3. Feedback, input and recommendations for patient education materials	What are your initial thoughts?	What did you learn? What did you already know? What was good/bad?
	What changes would you make?	Are there areas where information should be added? Are there areas were information is redundant/should be removed? Was anything unclear? Should anything be rephrased?

	What thoughts/feelings came up as you read through this document?	Was anything particularly striking? What emotions came up? (e.g. was anything worrying? Did anything make you feel empowered?)
	What feedback do you have on the graphic design of the document?	What did you think of the colours and images used? How did the design impact your experience reading the document? What did you think of the infographics used? Is there any information that would be better explained using an infographic?
	If you have SLE/if you had SLE, how likely would you be to seek additional information on cardiovascular disease?	Where would you get this information? (e.g. Google search, ask doctor, social media, etc.?)
SECTION 3: Online SLE-CALCULATOR tool		
Theme	**Question**	**Probe**
4. Feedback, input and recommendations for online calculator tool	Given the information discussed in the patient education resources, would you be interested in assessing your risk for cardiovascular disease?	Is this information important to you? Would this information change your daily habits/activities? Would you be interested in having your doctor/specialist assess your risk score?
	If a calculator were developed to assess your risk score for cardiovascular disease, what type of online platform would you prefer to use?	Website? App? Considerations for accessibility?
	What would indicate to you that this calculator is trustworthy?	University affiliation? Physician/researcher

		endorsement? Provided by your doctor?
	If you could access this calculator, what information do you think would be important to include with it?	e.g. Links to clinical studies? Resources about how to mitigate risks? Information about what risk scores mean?
CLOSING: • **Facilitator thanks participants and closes discussion**		

SEMI-STRUCTURED IN-DEPTH INTERVIEW GUIDE FOR PATIENTS

INTRODUCTION: Consent

[Facilitator reads:]

Thank you all for joining us today to speak about the SLE-CALCULATOR project. As a knowledge user, your insights are extremely valuable to helping us ensure this research is useful, useable and meaningful for the SLE community. Today, I will be facilitating a one-on-one interview on the development of the SLE-CALCULATOR tool and patient education materials describing the risks of cardiovascular disease in SLE.

Please be aware that this webinar will be audio and video recorded. You may choose to keep your camera on or turn it off for the duration of the webinar. No images will be used in any publications resulting from this research, but participating with the video may allow for better communication with the group. Excerpts from the webinar discussion may be included in any publications to come from this research, but any quotations will remain anonymous and your name, title, or any other indication of your identity will not appear. You may withdraw consent or leave the meeting at any time.

I want to remind you that there are no right or wrong answers, and we are interested in your honest opinions. If there are any questions you would prefer not to answer, simply say "pass". We ask that this conversation remains strictly confidential and will only be shared with the research team.

Before we get started, I ask that you confirm that you have read the information presented in the information letter, that you had the opportunity to ask any questions related to this study, to receive satisfactory answers to those questions, and to receive any additional details that you wanted.

[Participant confirms].

SECTION 1: Overview of the project

- Introductions of research team
- Overview of SLE-CALCULATOR project, research objectives, and deliverables

[Facilitator to pause and ask for any questions before proceeding.]

Theme	Question	Probe
1. Introduction/Background	First, I would like to remind you that you may use a pseudonym for confidentiality if you wish. What is your relationship with SLE?	When were you first diagnosed? How long have you been living with lupus?

		Do you participate in any SLE-related groups or events?
	What does lupus mean to you?	When you hear the word 'lupus', what comes to mind? What are some ways that SLE impacts your life?
SECTION 2: Lay patient education document		
Theme	**Question**	**Probe**
2. Knowledge, Attitudes and Practices	When you hear the term 'cardiovascular disease', what comes to mind?	What do you know about cardiovascular disease? What do you not know?
	What knowledge do you have about cardiovascular disease in the context of SLE?	Have you ever discussed this with your doctor? Have you come across this in your own searches for health information?
• Present document		
3. Feedback, input and recommendations for patient education materials	What are your initial thoughts?	What did you learn? What did you already know? What was good/bad?
	What changes would you make?	Are there areas where information should be added? Are there areas were information is redundant/should be removed? Was anything unclear? Should anything be rephrased?
	What thoughts/feelings came up as you read through this document?	Was anything particularly striking? What emotions came up? (e.g. was anything worrying? Did anything make you feel empowered?)

	What feedback do you have on the graphic design of the document?	What did you think of the colours and images used? How did the design impact your experience reading the document? What did you think of the infographics used? Is there any information that would be better explained using an infographic?
	How likely would you be to seek additional information on cardiovascular disease?	Where would you get this information? (e.g. Google search, ask doctor, social media, etc.?)
SECTION 3: Online SLE-CALCULATOR tool		
Theme	**Question**	**Probe**
4. Feedback, input and recommendations for online calculator tool	Given the information discussed in the patient education resources, would you be interested in assessing your risk for cardiovascular disease?	Is this information important to you? Would this information change your daily habits/activities? Would you be interested in having your doctor/specialist assess your risk score?
	If a calculator were developed to assess your risk score for cardiovascular disease, what type of online platform would you prefer to use?	Website? App? Considerations for accessibility?
	What would indicate to you that this calculator is trustworthy?	University affiliation? Physician/researcher endorsement? Provided by your doctor?
	If you could access this calculator, what information do you think would be important to include with it?	e.g. Links to clinical studies? Resources about how to mitigate risks? Information about what risk scores mean?
CLOSING: • **Facilitator thanks participant and closes the interview**		

APPENDIX E: Code book for focus group and interview analysis.

1. Identities

a) Sex/gender
- i) Female/woman
- ii) Male/man
- iii) Transgender
- iv) Other

b) Racial or ethnic background*
- i) Arab
- ii) Black
- iii) Asian
- iv) South Asian
- v) Southeast Asian
- vi) West Asian
- vii) Latinx
- viii) White
- ix) Indigenous
- x) Mixed
- xi) Other

c) Age
- i) 18-25
- ii) 25-35
- iii) 35-50
- iv) 50+

d) Education
- i) High school
- ii) College
- iii) University
- iv) Master's
- v) PhD
- vi) MD
- vii) Other

e) Key informant type **Focus group only*
- i) Lupus organization
- ii) Arthritis organization
- iii) CVD organization
- iv) Other health organization
- v) Physician
- vi) Researcher
- vii) Other

1. SLE

a) What does SLE mean to you?
b) Time living with SLE
c) Time to diagnosis
d) SLE impacts on life
    i) Physical impacts
    ii) Mental/psychosocial impacts
    iii) Family/relationships
    iv) Career
    v) Financial
    vi) Other
e) Participation in SLE-related activities
    i) SLE advocacy organizations
    ii) SLE events/fundraising
    iii) SLE support groups
    iv) Other
    v) No participation

2. Cardiovascular disease

a) Knowledge about CVD
    i) Heart/cardiovascular system
    ii) CVD risk factors
    iii) Lifestyle/prevention
    iv) CVD conditions
    v) Other
b) Knowledge gaps about CVD
c) CVD experiences
    i) Have had CVD experience
    ii) No CVD experience
    iii) At high risk
    iv) Other
d) Current lifestyle/behaviours
    i) Exercise
    ii) Diet
    iii) Smoking
    iv) Alcohol
    v) Risk monitoring
    vi) Other

3. Knowledge of SLE/CVD

- a) Knowledge about CVD/SLE
- b) Knowledge gaps about CVD/SLE
- c) Source of knowledge about CVD/SLE
    - i) Discussed with physician
    - ii) Did not discuss with physician
    - iii) Independent research
    - iv) Did not do research
    - v) CVD experience
    - vi) Other

4. Lay document

- a) Recommendations (Change)
    - i) Text
    - ii) Graphics
    - iii) Organization
    - iv) Other
- b) Positive feedback (Keep)
    - i) Text
    - ii) Graphics
    - iii) Organization
    - iv) Clarity/readability
    - v) Length/concise
    - vi) Other
- c) Thoughts/Feelings
    - i) Worry/concern
    - ii) Stress/anxiety
    - iii) Fear
    - iv) Empowerment
    - v) Other
- d) Impact on lifestyle
    - i) Likely to make changes
    - ii) Unlikely to make changes
    - iii) Will continue prevention
    - iv) Other
- d) Learnings/Takeaways

5. SLE-CALCULATOR

a) Interest in using SLE-CALCULATOR
    i) Yes
    ii) No
    iii) Other

b) Type of platform
    i) Website
    ii) App
    iii) Other

c) Indicators of trustworthiness
    i) Author information
    ii) Association with university/hospital
    iii) Association with advocacy organizations
    iv) Academic publications
    v) Endorsed by physician
    vi) Other

d) Accompanying information
    i) Instructions
    ii) Descriptions of variables
    iii) Meaning of risk score
    iv) Other resources
    v) Steps to reduce risk
    vi) Other

e) Impact on lifestyle
    i) Likely to make changes
    ii) Unlikely to make changes
    iii) Will continue prevention
    iv) Other

6. Other

APPENDIX F: Patient education resource reviewed in focus group and interviews.

Why are people with lupus at higher risk of developing cardiovascular disease?

It's still unclear exactly why people with lupus are at higher risk of developing CVD, but research provides us with some clues. Better treatments mean that people with lupus are living longer – however, this also means that as people age, their natural risk of CVD becomes greater, just like everyone else.[5] A risk factor is a trait, behavior or circumstance associated with a higher chance of developing CVD.

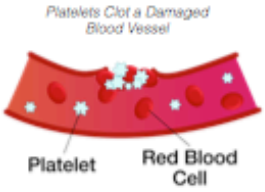
Risk Factors for the General Population

Additional Risk Factors for People with Lupus

Many of the CVD risk factors for people with lupus are the same as the general population:[5] having high cholesterol or high blood pressure, living with diabetes, having a family history of CVD, smoking, and older age[1] (being post-menopausal for women or older than 45 years for men). Research suggests that smoking is a particularly important CVD risk factor for people with lupus.[6]

There are also factors unique to lupus that increase risk of CVD. In lupus, the immune system is overactive, leading to inflammation in the body. This ongoing inflammation can speed up the process of atherosclerosis.[7] People with lupus may also have differences in the levels of substances in their blood, such as some types of lipids (fats) and antibodies, which also appear to contribute to atherosclerosis.[8,9]

People with lupus may also have differences in some types of blood cells. For example, platelets are a type of blood cell that forms blood clots. People with lupus tend to have platelets that are more active, and therefore tend to produce more clots.[10] When more clots are present, it becomes more likely that a clot could grow and eventually block blood flow.



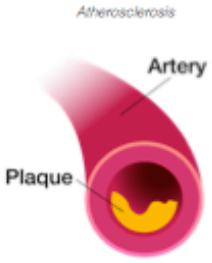
When blood flow is blocked, blood cannot travel to organs and tissues to deliver the oxygen they need to function. A heart attack happens when blood flow to the heart is blocked. When blood flow to the brain is blocked, a stroke can result.

Some medications may also contribute to the development of CVD. In many cases, lupus is treated using a type of drug called glucocorticoids (for example, prednisone is a glucocorticoid). In the short-term, glucocorticoids may protect against CVD. However, long-term use of glucocorticoids might further increase risk of CVD.[11] Other types of drugs, such as hydroxychloroquine (also called Plaquenil), appear to reduce risk of CVD.[12] If you are taking these medications, and do have questions or concerns, we recommend that you speak with your doctor about the benefits and risks of your treatment plan.

What is cardiovascular disease?

The cardiovascular system involves the heart and all the blood vessels in the body that circulate blood to and from muscles, organs, and other tissues. Cardiovascular disease (CVD) is an umbrella term that refers to a number of

conditions which that disrupt this system from functioning properly. Other common terms for CVD include heart disease, heart attack, stroke, and heart failure.[1]



CVD typically develops through a process called atherosclerosis. In atherosclerosis, a substance called plaque builds up on the walls of the arteries. Plaque is made up of fatty materials that collect on the artery walls, narrowing them, and preventing blood from flowing through. If the plaque grows over time and eventually blocks the artery, a heart attack or stroke can occur.[1]

People with lupus are at higher risk of developing CVD compared to people of the same age and sex who do not have lupus.[2,3] Being aware of and managing your risk of CVD is one important thing you can do to stay healthy.[4]

Who is most at risk?

In general, the risk of CVD increases with greater disease activity as well as age.[11] For example, there are high rates of CVD among patients with lupus nephritis, or kidney complications.[13] Black, Hispanic and other racial/ethnic minority populations may be at higher risk for more severe disease, and therefore CVD, as well.[14] Having a family history of parents, siblings or other close relatives with CVD may also increase your risk.[15]

As a person with lupus, what can I do to reduce my risk?

To reduce your risk of CVD, experts recommend the following:

Manage your lupus symptoms by following the treatment plan you and your doctor have created.[3,15]

Quit or cut down on smoking, vaping and tobacco use and reduce your exposure to cigarette smoke.[4,6]

Limit alcohol, as alcohol can increase blood pressure. A maximum of two drinks per day for men and one drink per day for women is recommended.[16]

Choose healthy foods and drinks: fresh fruits and vegetables and foods that are high in fiber and low in saturated fat, trans fats, processed sugars and cholesterol are best for heart health.[16]

Engage in regular physical activity: a total of 2 hours and 30 minutes per week of moderate exercise (walking, bicycling, sports, yoga, stretching, swimming, etc.) is recommended for healthy adults.[16] However, it's most important to listen to your body and make modiciations where necessary. Even small amounts of daily exercise or moving your body have been shown to have positive effects.

Reduce stress: identify what your stressors are and take action to manage them through activities like mindfulness, relaxation, practicing deep breathing, or seeking counselling or talk therapy.

Know your risk! Ask your doctor about monitoring your risk regularly.[8,15]

What research is being done to help?

Promoting cardiovascular health in people with lupus is an active area of research around the world. Currently, researchers from the University of Calgary, Harvard and MIT are working to develop an 'SLE calculator'. This calculator will be available online, and can be used to predict individuals' risk of CVD. Using the calculator will allow patients to better understand their personal risk of CVD, and monitor their risk over time. This will also allow healthcare providers to identify individuals who are most at risk, and better work with them to prevent CVD-related illness.

Participating in research studies is one important way that people living with SLE can contribute to improving quality of life for themselves and others. If you are interested in participating in research related to CVD for people with lupus, and/or development of the SLE calculator, please contact: [Contact person] or visit [Website] for more information.

For more information visit...

Our Partners

SLICC (Systemic Lupus International Collaborating Clinics Group) (https://sliccgroup.org/)
CanVECTOR (Canadian Venous Thromboembolism Research Network) (www.canvector.ca)

SLE & Related Organizations in Canada

Lupus Canada (https://www.lupuscanada.org/)
BC Lupus Society (https://www.bclupus.org/)
Lupus Society of Alberta (https://www.lupus.ab.ca/)
Lupus Saskatchewan (http://lupussk.com/)
Lupus Manitoba (https://lupusmanitoba.com/)
Lupus Ontario (https://www.lupusontario.org/)
Lupus Newfoundland & Labrador (https://www.lupusnl.com/)
Arthritis Society (www.arthritis.ca)

Global SLE Organizations

Lupus Foundation of American (www.lupus.org)
Lupus Europe (www.lupus-europe.org)

Cardiovascular Disease Resources

Heart & Stroke Foundation of Canada (https://www.heartandstroke.ca/)
Thrombosis Canada (www.thrombosiscanada.ca)
American Heart Association (www.heart.org)

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