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RELATIONSHIP BETWEEN NEIGHBORHOOD DEPRIVATION AND EPIGENETIC AGE ACCELERATION WITH PAIN IN ADULTS WITH MUSCULOSKELETAL PAIN

by

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A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
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RELATIONSHIP BETWEEN NEIGHBORHOOD DEPRIVATION AND EPIGENETIC AGE ACCELERATION WITH PAIN IN ADULTS WITH MUSCULOSKELETAL PAIN

PAMELA JACKSON

NURSING

ABSTRACT

Residents of high-deprivation neighborhoods shoulder a greater burden of age-related health conditions, including experiencing worse chronic musculoskeletal pain outcomes, compared to residents of more affluent neighborhoods. Advancing age is a risk factor for chronic health conditions, which epigenetic modifications may explain. Epigenetic age acceleration occurs when an individual's epigenetic age is older than their chronological age, and that discordance has been identified as a strong predictor of age-related conditions. Epigenetic age acceleration has also been correlated with neighborhood deprivation. However, the mechanisms for neighborhood disparities in chronic musculoskeletal pain remain unclear. The purpose of this dissertation study was to examine the relationship between neighborhood deprivation, chronic musculoskeletal pain outcomes, and epigenetic age acceleration in adults. This purpose was accomplished through three manuscripts: 1) a scoping review of neighborhood characteristics and epigenetic age acceleration, 2) a secondary analysis, methodological study comparing a measure of neighborhood deprivation with other measures of socioeconomic status among adults with chronic low back pain, and 3) a secondary analysis which explored whether epigenetic age acceleration mediated the relationship between neighborhood deprivation and pain severity in adults with knee osteoarthritis pain. In the main findings of this dissertation study (manuscript three), we found that increased neighborhood

deprivation was associated with increased pain severity and that epigenetic age acceleration may explain that relationship. These findings support future work on epigenetics and epigenetic age acceleration as a mechanism for the link between neighborhood and chronic musculoskeletal pain.

Keywords: neighborhood disparities, epigenetic aging, age-related health conditions, chronic musculoskeletal pain

DEDICATION

To

Emmy and Pavel

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"The things to do are: the things that need doing, that *you* see need to be done, and that no one else seems to see need to be done." ~ Buckminster Fuller

Thank you to my ancestors. You did what you knew to do. I promise to do the same. And to my chosen family Norman and Andrew, for seeing me through the dark times.

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INTRODUCTION

Aging is a significant risk factor for many diseases, including chronic pain. In fact, age-related health conditions are the leading causes of morbidity and mortality in the United States (U.S.) (Xu et al., 2020). Age-related health conditions are ailments whose prevalence increases as chronological age increases, typically emerging in middle age or older (Prasad et al., 2012). Chronic musculoskeletal pain is an age-related condition affecting about 1.7 billion people worldwide (Cieza et al., 2021; World Health Organization, 2022). Chronic low back pain (cLBP) and knee osteoarthritis (KOA) are common chronic musculoskeletal pain conditions estimated to impact 67% and 16% of older adults in the U.S., respectively (Deshpande et al., 2016; de Souza et al., 2019).

Chronic low back pain is defined as pain (either intermittent or continuous) that lasts 12 weeks or longer (Treede et al., 2015) and is associated with decreased productivity, major depression, and years lived with disability (Andersson, 1999; Gore et al., 2012; Hung et al., 2015; Stewart et al., 2003). Chronic low back pain also disrupts daily work and family activities and decreases the quality of life (Husky et al., 2018; Montgomery et al., 2016; Mutubuki et al., 2020). As cLBP severity increases, such disruptions likewise increase, with disability becoming more likely. Knee osteoarthritis is a degenerative joint disease (Hsu & Siwiec, 2022), with pain as the primary symptom (Favero et al., 2015; Neogi, 2013). Due to pain and concomitant stiffness, KOA is a major cause of disability (Litwic et al., 2013) that lowers the quality of life for those who

suffer from it (Kawano et al., 2015). In addition to tremendous suffering, cLBP and KOA produce combined annual expenses of over $340 billion in the U.S. in treatment costs and lost wages (Arthritis Foundation, 2019; Lo et al., 2021).

Like other age-related chronic conditions (Christine et al., 2017; Durfey et al., 2019; Mujahid et al., 2011; Mujahid et al., 2008; Xiao et al., 2018), chronic pain disproportionately affects residents of high-deprivation neighborhoods (Fuentes et al., 2007; Green & Hart-Johnson, 2012; Jordan et al., 2008), including a greater risk for KOA pain (Reyes et al., 2015). High-deprivation neighborhoods have a high concentration of poverty and lack socioeconomic resource-based indicators such as high levels of employment and good-quality housing. These neighborhoods also lack many characteristics of the built environment that are needed to live a healthy life—like safety (Clark et al., 2013; Loh et al., 2018) and walkability (Bereitschaft, 2017), as well as access to healthcare (Tsui et al., 2020), healthy foods (Hallum et al., 2020), and organized physical activities (Cohen et al., 2012). In addition to the influence of such neighborhood characteristics on health behaviors and access to care, the chronic stress of living in a low-resource community may exert a physiological toll that results in worse chronic pain outcomes (Bonathan et al., 2013).

Epigenetic modifications have been proposed as a possible mechanism for developing and maintaining chronic pain (Aroke et al., 2019; Buchheit et al., 2012; Denk & McMahon, 2012; Descalzi et al., 2015; Liang et al., 2015). Epigenetic mechanisms, such as DNA methylation (DNAm), are a way in which the external or internal environment may turn genes “on” or “off,” altering gene expression (Portela & Esteller, 2010). While differential DNAm plays a critical role in normal homeostasis, DNAm also

contributes to disease states (Robertson, 2005). So, variation in DNAm may explain variability in disease susceptibility (Aristizabal et al., 2020; Calvanese et al., 2009).

Differential DNAm has been shown to play a role in the pathophysiology of chronic pain (Descalzi et al., 2015; Liang et al., 2015). Several investigators have reported that differential DNAm of several genes has been associated with various pain conditions (Polli, Godderis, et al., 2020). For instance, *OPRM1* hypermethylation decreases opioid receptor expression. It predicts chronic postoperative pain (Chidambaran et al., 2017), while genes that control neuronal signaling (e.g., *BDNF*) and inflammation (e.g., *IL-17, TNF-*α) are differentially methylated in patients with fibromyalgia (Livshits et al., 2017; Polli, Ghosh, et al., 2020). Additionally, exposure to stressful environments such as situations of trauma, violence, and genocide has been associated with differential methylation, which explains susceptibility to pathological conditions such as depression and post-traumatic stress disorder (Morrison et al., 2019). This is salient because there is much overlap between stress and chronic pain (Abdallah & Geha, 2017), and residents of poor neighborhoods are exposed to more stress (Matheson et al., 2006; Steptoe & Feldman, 2001).

Age is a risk factor for chronic pain conditions (Kennedy et al., 2014), including cLBP (de Souza et al., 2019; Wong et al., 2017) and KOA (Blagojevic et al., 2010). In the U.S., the prevalence of cLBP among older adults ranges from 21%-70% (de Souza et al., 2019), and an estimated 37% of adults 60 years or older have KOA (Lawrence et al., 2008). However, chronological age may not represent the aging process precisely. While chronological age proceeds at a consistent rate for everyone (Beard & Bloom, 2015), individuals experience the aging process in different ways (Kotter-Grühn et al., 2015) and

at different rates (Ecker & Beck, 2019). Some septuagenarians may require assistance with activities of daily living (e.g., bathing, dressing), while others remain independent (Jylhävä et al., 2017). Compared to chronological age, which refers merely to the passage of time (Baker & Sprott, 1988; Hamczyk et al., 2020), biological age refers to physiological characteristics that indicate functional decline of the body. Biological age is postulated to be a more robust predictor of the health dimensions associated with advancing age (Ferrucci et al., 2020) and may predict the risk for age-related health conditions better than chronological age (Levine, 2013; Soriano-Tárraga et al., 2017).

Epigenetic age is an indicator of biological aging, capturing the impact of environmental factors across time on cellular and molecular function and potential disease risk (Hannum et al., 2013; Horvath, 2013). Several DNAm-based approaches have been used to estimate an individual's epigenetic age. Depending on the approach, epigenetic age is estimated based on the extent of methylation at dozens or even hundreds of cytosine-phosphate-guanine (CpG) sites across the genome. The estimated epigenetic age usually correlates with chronological age. However, sometimes there is a difference between epigenetic age and chronological age. Epigenetic age acceleration (EpAA) describes an individual's biological age advancing faster than their chronological age (Mendelson, 2018). Epigenetic age acceleration has been identified as a strong predictor of all-cause mortality (Marioni et al., 2015; Yan Zhang et al., 2017) and age-related health conditions (Hillary et al., 2020; Perna et al., 2016), including chronic pain (Cruz-Almeida et al., 2019). Additionally, EpAA is exhibited among people with a lower social position in society (Austin et al., 2018; Fiorito et al., 2019; Fiorito et al., 2017; Quach et al., 2017; Simons et al., 2016). Though EpAA has been observed in many age-related

diseases, it remains unclear whether EpAA can explain the relationship between neighborhood deprivation and outcomes in chronic musculoskeletal pain.

Problem Statement

Aging is an important risk factor for many chronic musculoskeletal pain conditions, including cLBP and KOA pain (Vos et al., 2012; World Health Organization, 2022). Over 60% of older adults in the U.S. experience cLBP (de Souza et al., 2019), and KOA pain impacts an estimated 16% of the older American population (Deshpande et al., 2016). People living in some neighborhoods experience more cLBP and KOA pain, with residents of high-deprivation neighborhoods exhibiting more severe and disabling chronic pain (Fuentes et al., 2007; Green & Hart-Johnson, 2012; Jordan et al., 2008). However, the physiological pathways for these disparities are not well understood. This lack of understanding limits effective pain management, increasing the burden of pain and the associated costs. While advancing age is known to increase the risk for chronic musculoskeletal pain (Vos et al., 2012; World Health Organization, 2022), people do not age at the same pace (Ecker & Beck, 2019; Kotter-Grühn et al., 2015). Studies of chronic pain outcomes and investigations on exposure to stress have revealed DNAm variation, supporting the notion that differential DNAm may play a role in interacting with these phenomena. Epigenetic age acceleration is a measure of biological age based on DNAm that correlates strongly with age-related diseases, including chronic pain. However, it remains unclear if EpAA explains the higher rates of chronic musculoskeletal pain in individuals living in high-deprivation neighborhoods.

Background and Significance

Chronic Low Back Pain Classification

Chronic low back pain is defined as pain in the lower back that lasts 12 weeks or longer and results in pain on at least half the days in the past 6 months (Deyo et al., 2014; Treede et al., 2015). While advancing age is a significant risk factor for cLBP, psychosocial factors such as level of education and anxiety are also known risk factors in the development of cLBP (Patrick et al., 2014). Chronic low back pain can be classified as either specific or non-specific, distinguished by the presence of a known pathophysiologic mechanism (e.g., disc herniation, osteoporosis) or the absence of such (Ronai & Sorace, 2013). Thus, non-specific cLBP is lower back pain that cannot be attributable to a known pathoanatomical condition. Diagnosis of non-specific cLBP is primarily based on history and clinical examination; imaging studies are not recommended because of inconsistency in findings (Balagué et al., 2012). The development of non-specific cLBP is not thought to arise from mechanical factors (i.e., strain from lifting or pulling); rather, genetic factors likely play a role (Balagué et al., 2012), and epigenetic modifications have been implicated as a biological mechanism underlying the genesis and maintenance of chronic pain (Liang et al., 2015). Older age is a risk factor for cLBP (Chou, 2021). In a systematic review evaluating 35 studies from 135,059 participants worldwide, de Souza and colleagues (2019) found that an estimated 21%-70% of older adults suffer from low back pain, including 67% of U.S. older adults. While chronological age is one of the most significant known risk factors for developing cLBP (Wong et al., 2017), whether EpAA plays a role in its pathology remains unexplored.

Knee Osteoarthritis Pain Classification

Knee osteoarthritis is a degenerative joint disease characterized by progressive wearing away of the articular cartilage and associated subchondral bone (Hsu & Siwiec, 2022; Litwic et al., 2013). Pain is the primary symptom of KOA (Favero et al., 2015; Neogi, 2013), which tends to develop gradually and worsen over time (Hsu & Siwiec, 2022). Diagnosis can be made based on patient history and clinical features such as pain, morning stiffness, and crepitus with movement (Heidari, 2011a). Radiographic studies or magnetic resonance imaging may also be useful to determine the extent of the disease, such as the degree of joint involvement (e.g., bony enlargement) (Heidari, 2011a). Associated with the pain and stiffness characteristic of the disease, KOA is a major cause of disability (Cross et al., 2014), resulting in reduced quality of life for its sufferers (Kawano et al., 2015). Knee osteoarthritis is most likely to occur in older adults (Heidari, 2011b; Hsu & Siwiec, 2022), affecting approximately 16% of older U.S. adults. However, while chronological age as a risk factor is well known, recent evidence suggests that EpAA may also be a factor. In a comparison of adults with and without KOA pain, Cruz-Almeida et al. (2022) found that, on average, participants suffering from KOA pain exhibit significantly increased EpAA compared to the individuals without pain (5.34 ± 0.41 vs. 1.12 ± 0.30, $p = 0.007$).

Neighborhood Deprivation and Chronic Musculoskeletal Pain

To explore the relationship between neighborhood deprivation, chronic musculoskeletal pain, and EpAA, an understanding of neighborhood deprivation is needed. A neighborhood refers to a spatially defined area that constitutes an individual's

immediate residential environment created by a context of shared needs and opportunities (Chaskin, 1997; Diez Roux, 2001). Neighborhood deprivation refers to unfavorable physical and perceived characteristics of a neighborhood, such as low access to greenspace, physical activity facilities, and healthy food outlets, as well as decreased safety, poor quality housing, and a concentration of people with low socioeconomic status (SES) (Mouratidis, 2020; Ribeiro et al., 2018). Neighborhood deprivation has been linked to worse health outcomes, including central obesity (Hu et al., 2021), diabetes (Hu et al., 2021), breast cancer (Saini et al., 2019), the incidence of hypertension (Claudel et al., 2018), and the management of chronic conditions (Durfey et al., 2019).

Investigations of the impact of neighborhood deprivation on chronic musculoskeletal pain are a reasonably recent phenomenon, with the first study located in the literature published in 2002 (Brekke et al., 2002). The consensus across studies on musculoskeletal pain is that neighborhood deprivation is associated with worse pain outcomes (Giummarra et al., 2018; Jonsdottir et al., 2019; Jordan et al., 2008; Leue et al., 2012). For example, Ulirsch et al. (2014) found that, among 948 U.S. adults who had been involved in a motor vehicle accident, living in higher-deprivation neighborhoods was associated with greater musculoskeletal pain and interference with daily activities. Similarly, in a population-based study of 74,217 adults who had survived a vehicular crash, Giummarra et al. (2018) found that those living in higher-deprivation areas had greater rates of developing chronic pain than those living in lower-deprivation areas. This relationship holds for cLBP and KOA specifically as well. Yu and colleagues (2021) reported that among 72,009 individuals who were part of population-based general practices in the UK, a higher percentage of adults who sought treatment for moderate to

severe cLBP resided in high-deprivation neighborhoods (36.3%) in comparison to residents of the least deprived neighborhoods (24.8%). Similarly, in a population-based study including records for over 5 million residents of Catalonia, Spain, Reyes and colleagues (2015) reported that those living in the most deprived neighborhoods had an increased risk of KOA (Incidence Rate Ratio 1.51 [1.45-1.57]) compared to those living in the least deprived neighborhoods.

Epigenetics and Epigenetic Modifications

Epigenetics is the study of heritable changes in chromatin and gene expression without alterations in the underlying DNA sequence (Dupont et al., 2009). It examines how environmental stimuli change chromatin structure and function of cells to retain memories of past exposures. While there are several epigenetic changes (e.g., miRNA, long non-coding RNA, histone modifications), DNA methylation is the most well-studied epigenetic change (Lowe et al., 2015). DNA methylation refers to the covalent addition of a methyl group to the cytosine nucleotide of a DNA molecule. While some cytosine nucleotides on some genes (or segments of genes) are normally methylated, exposure to internal and external stimuli can change the level of DNA methylation, resulting in hyper or hypomethylated regions (Meaney, 2010). When hyper- or hypomethylation occurs at CpG sites (especially at CpG islands in the promotor region of a gene), these changes in DNAm may alter gene expression, thereby affecting gene function, with subsequent changes in the production of proteins controlled by the associated genes (Brockie et al., 2013). In this way, changes in the profile of DNA methylation may alter health outcomes (Brockie et al., 2013) and could help explain health disparities.

Differential DNA methylation has been shown to play a role in the mechanisms of chronic pain (Descalzi et al., 2015; Liang et al., 2015), and emerging evidence also suggests there are environmental differences in DNA methylation (Buchheit et al., 2012), which may explain neighborhood disparities in pain (Green & Hart-Johnson, 2012; Maly & Vallerand, 2018). Several investigators have reported differential DNAm of candidate genes as well as epigenome-wide differences in individuals with chronic pain (Achenbach et al., 2019; Bell et al., 2014; Chidambaran et al., 2017; Ciampi de Andrade et al., 2017; Gombert et al., 2019; Li Yim et al., 2016; Menzies et al., 2013; Sukenaga et al., 2016; Takenaka et al., 2020), including cLBP and KOA. This topic is discussed in more detail below.

Epigenetics and Chronic Pain

A growing body of literature is uncovering epigenetic mechanisms for the pathogenesis of chronic pain, particularly about DNAm differences. With regards to candidate gene studies, findings suggest that differences in the DNAm of specific genes related to pain are associated with pain conditions (Achenbach et al., 2019; Chidambaran et al., 2017; Gombert et al., 2019; Sukenaga et al., 2016; Takenaka et al., 2020). To date, most candidate gene studies on chronic pain have focused on two candidate genes, in particular: transient receptor potential ankyrin 1 (*TRPA1*) and mu-opioid receptor 1 (*OPRM1*), which play a role in pain modulation and analgesia (Peciña et al., 2015; Souza Monteiro de Araujo et al., 2020). The consensus among studies about DNAm of the *TRPA1* gene and pain is that pain is associated with hypermethylation of CpG sites of the *TRPA1* gene (Achenbach et al., 2019; Gombert et al., 2019; Sukenaga et al., 2016;

Takenaka et al., 2020). For example, Sukenaga et al. (2016) found an increase in DNAm of the *TRPA1* gene at the cg01610488, chr8: 72987870 CpG island is significantly associated with an increase in the number of neuropathic pain symptoms ($r = 0.82$, $p = 0.001$). Similarly, Chidambaran et al. (2017) found that methylation of the *OPRM1* gene at CpG sites 13 ($r = 0.067$) and 22 ($r = 0.036$) is associated with chronic post-surgical pain ($p < 0.05$). However, not all studies agree. Hatfield et al. (2018) reported no difference in DNAm at the 5' end of the *OPRM1* gene when comparing healthy infants with infants exposed to painful stimuli (as part of treatment during admission to the neonatal intensive care unit).

Epigenome-wide association studies reveal differences in DNAm when comparing participants with a pain condition and healthy controls (Bell et al., 2014; Burri et al., 2016; Ciampi de Andrade et al., 2017; Li Yim et al., 2016; Menzies et al., 2013). For example, when comparing patients with Crohn's disease and age and gender-matched healthy controls, Li Yim et al. (2016) identified 4,287 differentially methylated positions (Benjamini-Hochberg corrected $p < 0.05$) located on genes that are enriched to immune response processes and inflammatory pathways. Another study by Ciampi de Andrade et al. (2017) found 1,610 differentially methylated positions (FDR < 0.05, delta-beta > 5%) between patients with fibromyalgia and healthy controls. These differentially methylated positions are associated with genes enriched in stress response pathways. Since chronic pain and stress are linked (Abdallah & Geha, 2017), enrichment of genes in stress response pathways supports the premise that the stress associated with living in high-deprivation neighborhoods could result in DNAm differences that impact pain outcomes.

Epigenetics of Chronic Low Back Pain and Knee Osteoarthritis

Regarding cLBP, in an epigenome-wide association study investigating DNAm differences in 50 adults with cLBP in comparison to 49 healthy controls, our team found 159 differentially methylated regions ($q < 0.01$, methylation difference > 10%) and that most of these regions are located in genes that function in biological processes associated with immune signaling, endochondral ossification (which is involved in bone formation during fracture healing), and G-protein coupled transmissions (G-proteins are involved in pain modulation) (Aroke et al., 2020). Another epigenome-wide study ($n = 32$) detected DNAm differences between groups of individuals with pain compared to pain-free controls, with 2,496 differentially methylated CpG sites found in women and 419 in men (Grégoire et al., 2021). Gene enrichment analysis of the differentially methylated sites revealed the associated genes had functions related to the histocompatibility complex (which plays a major role in the immune system) and DNA methyltransferases (enzymes that mediate the addition of a methyl group to a cytosine molecule (Grégoire et al., 2021; Lanata et al., 2018). In a candidate gene study, Tajerian and colleagues (2011) found that patients with severe low back exhibited increased methylation in the promoter region of the secreted protein, acidic, rich in cysteine (*SPARC*) gene compared to pain-free controls ($p < 0.05$). The SPARC protein functions in bone formation and wound healing (Bradshaw & Sage, 2001) and may be important in the pathogenesis of cLBP.

Hundreds of studies have been conducted on epigenetics and KOA in the last 5 years alone (Peffers et al., 2018; Reynard & Barter, 2020; Young et al., 2022). So, the following discussion on the epigenetics of KOA will be limited to an introduction to studies on DNAm. Most studies of DNAm and KOA have been conducted using

cartilage, subchondral bone, or synovium (Visconti et al., 2021). For example, Zhang and colleagues (2016) detected differentially methylated positions in the subchondral bone from knee joints of individuals with early-stage versus late-stage KOA. In their comparison, 397 significantly differentially methylated positions covering 135 genes were identified, 41.8% hypomethylated and 58.2% hypermethylated (Yanfei Zhang et al., 2016). Another study, by Aref-Eshghi et al. (2015), reported 72 differentially methylated regions in comparing knee cartilage from participants with KOA and cartilage from osteoarthritis-free controls. The identified regions were located in genes significantly enriched in skeletal system morphogenesis and development, suggesting a role in KOA pathophysiology (Aref-Eshghi et al., 2015). However, since this dissertation work examined the relationship between KOA pain and EpAA using epigenetic age estimated from DNA derived from peripheral whole blood, special attention was placed on locating studies that did *not* investigate DNAm differences in other tissues (e.g., cartilage).

Interestingly, there has been a lack of studies using peripheral blood to examine DNAm in KOA compared to osteoarthritis-free or knee pain-free participants. The first investigation appeared in the literature in 2019 (Dunn et al., 2019). In this study, based on a sample of 58 adults with progressively worsening KOA and 58 matched controls with KOA that was not progressing (as classified by radiograph), Dunn and colleagues (2019) determined that a DNAm-based model could distinguish between the progressors and non-progressors (Odds Ratio = 11 ± 2). While this study supports a link between KOA and DNAm, as the sole report, it can only demonstrate promise for future studies that will increase our understanding of KOA pathophysiology through investigating DNAm

differences. A discussion of the more specific relationship between epigenetic age and KOA is presented later.

Epigenetic Age and Epigenetic Age Acceleration

Even though chronological age is a risk factor for chronic pain (Kennedy et al., 2014), including cLBP (de Souza et al., 2019; Wong et al., 2017) and KOA (Heidari, 2011b), biological age is postulated to be a more robust predictor of the health dimensions associated with advancing age (Ferrucci et al., 2020), including morbidity and mortality (Levine, 2013; Soriano-Tárraga et al., 2017). Epigenetic age is an indicator of biological aging that captures the impact of environmental factors across time on cellular and molecular function and potential disease risk (Hannum et al., 2013; Horvath, 2013). Several approaches (also called "clocks") have been developed that use levels of DNAm at selected CpG sites to estimate an individual's epigenetic age. Sometimes there is a difference between epigenetic age and chronological age. Epigenetic age acceleration describes a phenomenon where an individual's biological age is higher than their chronological age, whereas the opposite signifies inverse or slower epigenetic age acceleration (Mendelson, 2018). Studies have suggested that EpAA is a strong predictor of all-cause mortality (Marioni et al., 2015; Yan Zhang et al., 2017) and age-related health conditions (Hillary et al., 2020; Horvath & Raj, 2018; Irvin et al., 2018; Perna et al., 2016), including chronic pain (Cruz-Almeida et al., 2019). Additionally, EpAA was reported to be associated with a lower social position in society (Austin et al., 2018; Fiorito et al., 2017; Simons et al., 2016).

Epigenetic Age and Chronic Musculoskeletal Pain

To date, few studies have investigated epigenetic age and chronic musculoskeletal pain, with only one study specifically involving KOA (Cruz-Almeida et al., 2022) and none examining cLBP. Studies that have examined EpAA and musculoskeletal pain have had conflicting results. In a study of 29 older adults with and without chronic pain, Cruz-Almeida et al. (2019) found that participants with chronic pain ($n = 20$) had "older" epigenetic age than participants without chronic pain ($n = 9$, $p < 0.05$). Another study by researcher Cruz-Almeida (2022) reported a link between EpAA and KOA pain outcomes in a larger, more diverse sample of participants ($n = 213$). Specifically, participants with more disabling knee pain on average were epigenetically older by 3.6 years compared to those with less disabling knee pain and 4.2 years older than pain-free controls, using the GrimAge clock ($p < 0.01$). In contrast, Kwiatkowska et al. (2020) found no statistically significant difference in EpAA between participants with various pain conditions (fibromyalgia, migraine, and medication overuse headache) compared to healthy controls. Interestingly, these investigators used five different epigenetic clocks, including the Horvath clock (Kwiatkowska et al., 2020).

Epigenetic Age Acceleration and Neighborhood Deprivation

While the relationship between neighborhood deprivation and epigenetic age is a burgeoning area of study, overall, the evidence suggests that there is an association between EpAA and neighborhood deprivation in adults (Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Martin et al., 2021; Ward-Caviness et al., 2020). In a study of 100 Black women, Lei et al. (2019) found that neighborhood deprivation is significantly

associated with EpAA (ß = 0.237, p = 0.023). Likewise, Lawrence et al. (2020) reported that among 2,630 White women, those with the greatest neighborhood deprivation (>75th percentile) had higher EpAA compared to those with the least (25th percentile) neighborhood deprivation (ß = 0.23; 95% CI 0.01 – 0.45). Another recent study by Ward-Caviness et al. (2020) added to the evidence, reporting an 0.15 effect estimate (95% CI 0.06 – 0.25, p = 0.002), whereby neighborhood characteristics such as the presence of abandoned cars, streets in poor condition, non-art graffiti, and alcohol advertising were associated with an increase in residents' epigenetic aging score.

Summary

People living in high-deprivation neighborhoods experience more severe and disabling chronic musculoskeletal pain (Giummarra et al., 2018; Jonsdottir et al., 2019). Chronic low back pain and KOA pain are chronic musculoskeletal pain conditions commonly affecting older adults (Deshpande et al., 2016; de Souza et al., 2019). Low back pain is considered chronic when it lasts 12 weeks or longer and results in pain on at least half the days in the past 6 months (Treede et al., 2015). Knee osteoarthritis is a degenerative joint disease characterized by progressive wearing away of the articular cartilage and associated subchondral bone (Hsu & Siwiec, 2022; Litwic et al., 2013). Both cLBP and KOA are often diagnosed based on patient history and clinical examination (Balagué et al., 2012; Heidari, 2011a). Epigenetic mechanisms for the pathogenesis of chronic pain (Descalzi et al., 2015; Liang et al., 2015), including cLBP (Aroke et al., 2020) and KOA (Peffers et al., 2018; Reynard & Barter, 2020; Young et al., 2022) are being revealed. Epigenetic age is an indicator of biological aging that captures the impact of environmental factors on epigenetic changes and potential disease risk

(Horvath & Raj, 2018). As such, the pace of epigenetic aging may reflect the impact of neighborhood environmental exposures on chronic musculoskeletal pain. Epigenetic age acceleration is a phenomenon where an individual's biological age is older than their chronological age (Mendelson, 2018). Epigenetic age acceleration is a strong predictor of all-cause mortality and age-related health conditions (Hillary et al., 2020; Marioni et al., 2015; Perna et al., 2016), including chronic pain (Cruz-Almeida et al., 2019). Epigenetic age acceleration is also associated with neighborhood deprivation in adults (Lawrence et al., 2020; Lei et al., 2022). However, whether EpAA may explain the relationship between neighborhood deprivation and chronic musculoskeletal pain outcomes remains unexplored.

Purpose

The purpose of this dissertation was to examine the relationship between neighborhood deprivation, chronic musculoskeletal pain outcomes, and EpAA in adults. This was achieved through the production of three papers that include a scoping review of neighborhood characteristics and EpAA, a methodological paper comparing a measure of neighborhood deprivation with other measures of SES among adults with cLBP, and a paper reporting a mediation analysis study of the relationship between neighborhood deprivation and KOA pain severity by EpAA.

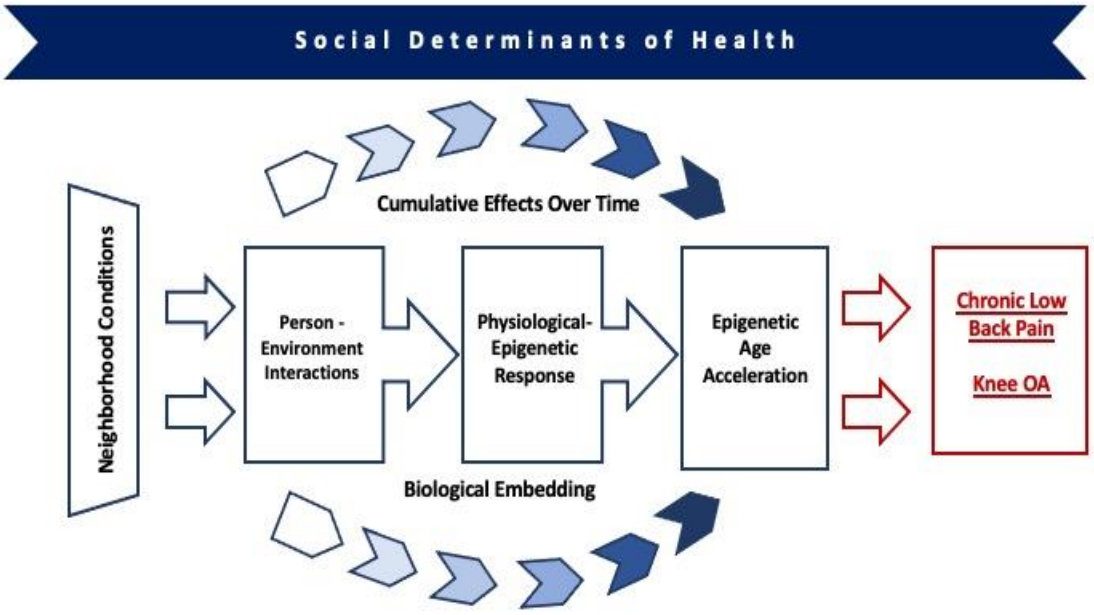
Conceptual Framework

This dissertation is guided by Geronimus' Weathering Hypothesis, which asserts that social marginalization exerts "wear and tear" on the body, leading to health

deterioration (Geronimus et al., 2010) and so may explain accelerated aging. Originally developed to explain disparate health outcomes in young African American mothers, the Weathering Hypothesis has since been tested in studies on inflammation (Schmeer & Tarrence, 2018; Simons, Lei, Klopack, Zhang, et al., 2021), disability (Chinn & Hummer, 2016; Lin & Kelley-Moore, 2017), and epigenetic age (Brody et al., 2016; Simons et al., 2016; Simons, Lei, Klopack, Beach, et al., 2021) and in different populations (Collins et al., 2012; Wildsmith, 2002). Underlying both our central hypothesis and Geronimus' Weathering Hypothesis is the concept of the social determinants of health (SDOH). The World Health Organization (n.d.) defines SDOH as the conditions in which people live, work, play, and grow. These conditions deeply influence health outcomes by shaping health behaviors and determining daily exposures to environmental stressors (Artiga & Hinton, 2018; Braveman & Gottlieb, 2014). Our central hypothesis (Figure 1) asserts that, due to social marginalization, residents of high-deprivation neighborhoods frequently experience higher levels of stress from person-environment interactions. The experience of interacting with high deprivation and/or discriminatory environment leads to physiological responses (Allen et al., 2019; Hackman et al., 2019; Kim et al., 2020; Leite et al., 2019; Sawyer et al., 2012). Epigenetic modifications (such as DNAm) induce changes at the cellular and molecular levels (Tammen et al., 2013; Tollefsbol, 2004). Over time, this chronic stress exerts "wear and tear" on the body through epigenetically induced physiologic adaptation and maladaptation, resulting in EpAA and subsequent worse chronic musculoskeletal pain outcomes.

Figure 1

Chronic Low Back Pain Weathering Hypothesis Theoretical Framework



Overview of the Three Manuscripts

Manuscript 1 – Neighborhood Environment and Epigenetic Age: A Scoping Review

The purpose of manuscript one was to appraise the scientific literature on the relationship between the neighborhood environment and epigenetic age. Neighborhoods are multidimensional in nature, composed of social and physical characteristics, including environmental exposures (Diez-Roux, 2016). Accordingly, various neighborhood characteristics have been studied and associated with several age-related health conditions, including chronic pain. To capture the breadth of the neighborhood environment that may be influencing epigenetic age, the goal of manuscript one was to explore the relationship between the neighborhood environment and epigenetic age

without limiting the type of neighborhood characteristic. A scoping review methodology, as described by Arksey and O'Malley (2005), was used to address the following specific aim and research questions:

Specific Aim 1: Examine the literature about the relationship between neighborhood characteristics and epigenetic age.

Research Question 1a. What does the current literature reveal about the presence of a relationship between neighborhood characteristics and epigenetic age?

Research Question 1b. How have neighborhood characteristics and epigenetic age been measured in studies on the relationship between neighborhood characteristics and epigenetic age?

Research Question 1c. What are the current gaps in the literature on the relationship between neighborhood characteristics and epigenetic age?

Scoping reviews are most appropriate when the literature is heterogenous in nature or when the review's goal includes identifying gaps in the research (Peters et al., 2015). Considering that (a) this review encompassed a range of neighborhood characteristics, (b) there are multiple epigenetic clocks available to measure epigenetic age (Horvath & Raj, 2018), and (c) one of the research questions was to identify gaps in the research, a scoping review was the ideal methodology.

Manuscript 2 – The Area Deprivation Index Corresponds Effectively With Other Measures of Objective Socioeconomic Status in Adults With Chronic Low Back Pain

The purpose of manuscript two was to compare neighborhood deprivation with other measures of SES in predicting pain severity and interference in adults with cLBP. This methodological study employed a secondary analysis of data collected for an

ongoing study: Examining Racial and SocioEconomic Disparities in Chronic Low Back Pain (ERASED) (R01MD010441). The ERASED project aims to characterize racial differences in cLBP outcomes using a socioeconomic framework. Manuscript two employed a correlational design to examine the relationships under study. Multiple correlational designs allow for the assessment of relationships between several variables that are not amenable to manipulation (Polit & Beck, 2017). Since SES characteristics are not immediately amenable to experimental manipulation, a correlational design was best for this study. The specific aim and research questions included:

Specific Aim 2: Compare the Area Deprivation Index (ADI) with income, education, and subjective social status in predicting pain severity and interference in adults with cLBP.

Research Question 2a: How well does the area-level measure of SES (ADI) predict cLBP severity and interference compared to individual-level measures of SES (income, education, subjective social status)?

Research Question 2b: How well do objective measures of SES (ADI, income, education) predict cLBP severity and interference compared to a subjective measure of SES (subjective social status)?

Manuscript 3 – Epigenetic Age Acceleration Mediates the Relationship Between Neighborhood Deprivation and Pain Severity in Adults with Knee Osteoarthritis

The purpose of manuscript three was to examine the relationship between neighborhood deprivation and pain severity in KOA and the influence of EpAA on that relationship. This study used a correlational and causal mediation design based on a secondary analysis of data collected as part of the Understanding Pain and Limitations in Osteoarthritic Disease (UPLOAD-2) study. First, correlations between neighborhood

deprivation, KOA pain severity, and EpAA were performed to create a foundational understanding of the relationships' presence, strength, and direction before exploring a potential causal relationship. Mediation analysis tests a hypothetical causal chain, quantifying the extent and significance of the effect of one variable (predictor) on a second variable (mediator) and, in turn, affecting a third (outcome) variable (MacKinnon et al., 2007). It tests possible causal relationships (Zhao et al., 2010). As such, mediation analysis was the ideal method to determine if neighborhood deprivation affects KOA pain severity through the influence of EpAA.

Specific Aim 3: Examine the correlations between neighborhood deprivation, KOA pain severity, and EpAA.

Research Question 3: In adults with KOA, how are neighborhood deprivation, pain severity, and EpAA correlated with each other?

Specific Aim 4: Investigate whether EpAA explains the relationship between neighborhood deprivation and KOA pain severity.

Research Question 4: In adults with KOA, does EpAA explain the relationship between neighborhood deprivation and pain severity?

Summary

This dissertation examines the relationship between neighborhood deprivation, chronic musculoskeletal pain (cLBP and KOA pain), and EpAA. Chapter 1 described the problem, background, and conceptual framework guiding this three-manuscript-based dissertation. Additionally, this chapter provided an overview of the specific aims and research questions for each manuscript (presented in chapters 2 through 4) and definitions

of key terms. Chapter 5 combines the findings from all three manuscripts, offers a comprehensive interpretation, and provides recommendations for future research.

Key Terms

This section provides definitions for key terms used throughout the dissertation.

Age-related health conditions are diseases or conditions whose occurrence increases with age (Franceschi et al., 2018; Jaul & Barron, 2017).

Biological age refers to physiological characteristics that indicate a functional decline of the body, compared to chronological age, which refers merely to the passage of time (Baker & Sprott, 1988; Hamczyk et al., 2020).

Chronic low back pain is pain located in the lower back that lasts (either continuously or intermittently) for 12 weeks or longer (Treede et al., 2015).

Chronic musculoskeletal pain is continuous or intermittent pain that stems from a pathophysiological process affecting the muscle, bone, joint, or associated soft tissue (Treede et al., 2015).

Chronic pain is continuous or intermittent pain that lasts 3 months or longer (Treede et al., 2015).

DNA methylation is an epigenetic mechanism that regulates gene expression by transferring a methyl group onto the C-5 position of the cytosine ring of DNA (Moore et al., 2013).

Epigenetic age is a measure of biological age as calculated by an epigenetic clock (Horvath & Raj, 2018).

Epigenetic age acceleration describes an individual's epigenetic/biological age that is advancing faster than their chronological age (Horvath & Raj, 2018; Mendelson, 2018).

Epigenetic changes (or modifications) are stable and heritable alterations to the chromosome, which occur primarily from environmental exposures and do not alter DNA sequence (Aristizabal et al., 2020).

Epigenetic clocks use patterns of DNA methylation levels in the genome to measure epigenetic age (Bell et al., 2019).

Epigenetics is the study of mechanisms (including DNA methylation, histone modifications, and non-coding RNA) that regulate gene expression (Handy et al., 2011).

Knee osteoarthritis is a degenerative disease of the knee joint characterized by wear and tear of the articular cartilage and associated subchondral bone (Hsu & Siwiec, 2022; Li et al., 2013). The hallmark feature of KOA is pain (Favero et al., 2015).

Knee osteoarthritis pain is characterized as developing gradually, worsening with activity, and being accompanied by stiffness and swelling (Hsu & Siwiec, 2022).

Neighborhood refers to a spatially defined area that constitutes an individual's immediate residential environment created by a context of shared needs and opportunities (Chaskin, 1997; Diez Roux, 2001).

Neighborhood deprivation refers to unfavorable physical and perceived characteristics of a neighborhood, such as low access to greenspace, physical activity facilities, and healthy food outlets, as well as decreased safety, poor-quality housing, and a concentration of people with low SES (Mouratidis, 2020; Ribeiro et al., 2018).

Pain interference refers to the extent that pain limits an individual's ability to engage in physical, mental, and social activities (Amtmann et al., 2010).

Pain severity refers to the level of intensity of pain experienced (Cleeland & Ryan, 1994). *Social marginalization* is defined as the process of individuals or groups being figuratively pushed to the periphery or margins of a society or social network based on perceived unacceptable characteristics such as race, gender, politics, culture, or economics (Hall et al., 1994).

NEIGHBORHOOD ENVIRONMENT AND EPIGENETIC AGE: A SCOPING REVIEW

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NEIGHBORHOOD ENVIRONMENT AND EPIGENETIC AGE: A SCOPING REVIEW

For decades, there has been increasing interest in how social conditions become biologically embedded, impacting health and disease risk (Hertzman, 2012). It has become increasingly clear that social circumstances such as neighborhood environment are associated with age-related chronic conditions. Specifically, the burden of age-related chronic conditions disproportionately affects individuals living in high-deprivation neighborhoods (Christine et al., 2017; Durfey et al., 2019; Mujahid et al., 2011; Xiao et al., 2018). High-deprivation neighborhoods are geographic areas characterized by socioeconomic indicators such as high unemployment and poverty and low educational attainment (Mouratidis, 2020; Ribeiro et al., 2018). These neighborhoods often lack resources needed to live a healthy life, like walkability (Bereitschaft, 2017), access to healthy foods (Hallum et al., 2020), health care (Tsui et al., 2020), and safety (Clark et al., 2013; Loh et al., 2018). Neighborhoods with lower education levels have been linked to a higher risk for stroke and myocardial infarction (Pedigo et al., 2011), and higher levels of neighborhood deprivation correlate with increases in chronic low back pain severity (Jackson et al., 2021). In addition to experiencing a greater burden of multiple chronic conditions, residents of high-deprivation neighborhoods are more likely to carry this burden even after controlling for other socioeconomic status measures (Chamberlain et al., 2020). Furthermore, residents of high-deprivation neighborhoods can have lifespans up to 20 years shorter than those residing in different neighborhoods in the same city (Holmes et al., 2018; LeCounte & Swain, 2017; Robert Wood Johnson Foundation, 2015).

The relationship between high-deprivation neighborhoods and age-related chronic conditions is complex and impacted by many factors. Beyond a lack of socioeconomic resources, residents of high-deprivation neighborhoods are disproportionately exposed to adverse environmental factors like greater noise (Casey et al., 2017; Dale et al., 2015), increased air pollution (Colmer et al., 2020; Hajat et al., 2013), higher ambient heat (Chakraborty et al., 2019), and less vegetation (McDonald et al., 2021; Nesbitt et al., 2019; Schwarz et al., 2015). These neighborhood characteristics have been linked to poorer health-related outcomes in age-related conditions (Beulens et al., 2022; Brook et al., 2004; Malambo et al., 2016; Münzel et al., 2014; Wang et al., 2019), yet research on the exact biological mechanisms underlying this relationship remains inconclusive.

Even though advancing age is a crucial determinant of age-related conditions, emerging evidence suggests that biological age, such as epigenetic age, is a better predictor of age-related morbidity (Horvath & Raj, 2018). Because epigenetic changes are environmentally sensitive changes in gene expression, epigenetic age captures the impact of environmental factors across time on cellular and molecular function and potential disease risk (Hannum et al., 2013; Horvath, 2013). Several approaches (also called “clocks”) have been developed to estimate an individual’s epigenetic age based on DNA methylation patterns, which usually correlate with chronological age. However, sometimes there is incongruency between epigenetic age and chronological age. For example, epigenetic age acceleration occurs when an individual’s epigenetic age is advancing faster than their chronological age. It has been suggested that EpAA may serve as a biomarker of the degree of wear and tear that the body has experienced (Mendelson, 2018). In support of this perspective, epigenetic age acceleration has been identified as a

strong predictor of age-related conditions (Hillary et al., 2020; Horvath & Raj, 2018; Irvin et al., 2018; Perna et al., 2016; Pottinger et al., 2021) and all-cause mortality (Marioni et al., 2015; Zhang et al., 2017).

The literature demonstrates a link between neighborhood residence and age-related health conditions and a clear connection between epigenetic age acceleration and age-related health conditions. However, it remains unclear which neighborhood characteristics correlate with epigenetic age and whether specific epigenetic clocks better predict age-related chronic health conditions. To our knowledge, no review has examined the relationship between neighborhood characteristics and epigenetic age with the goal of capturing various aspects of the neighborhood setting beyond socioeconomic status. Thus, there is a need to map neighborhood characteristics in relation to epigenetic aging, including the nature of the relationship. To address this need, we used a scoping review methodology to answer the following research questions: (a) What does the current literature reveal about the relationship between neighborhood characteristics and epigenetic age? (b) In studies of this relationship, how have neighborhood characteristics and epigenetic age been measured? (c) What are the gaps in the research?

Methods

We used the framework developed by Arksey and O'Malley (2005) to conduct this scoping review. This method has been used to identify the extent of a body of research on a topic and/or gaps in the evidence base (Arksey & O'Malley, 2005; Lockwood et al., 2019). Neighborhoods are small spatially-defined residential areas comprised of a number of both social and physical characteristics (Chaskin, 1997; Diez

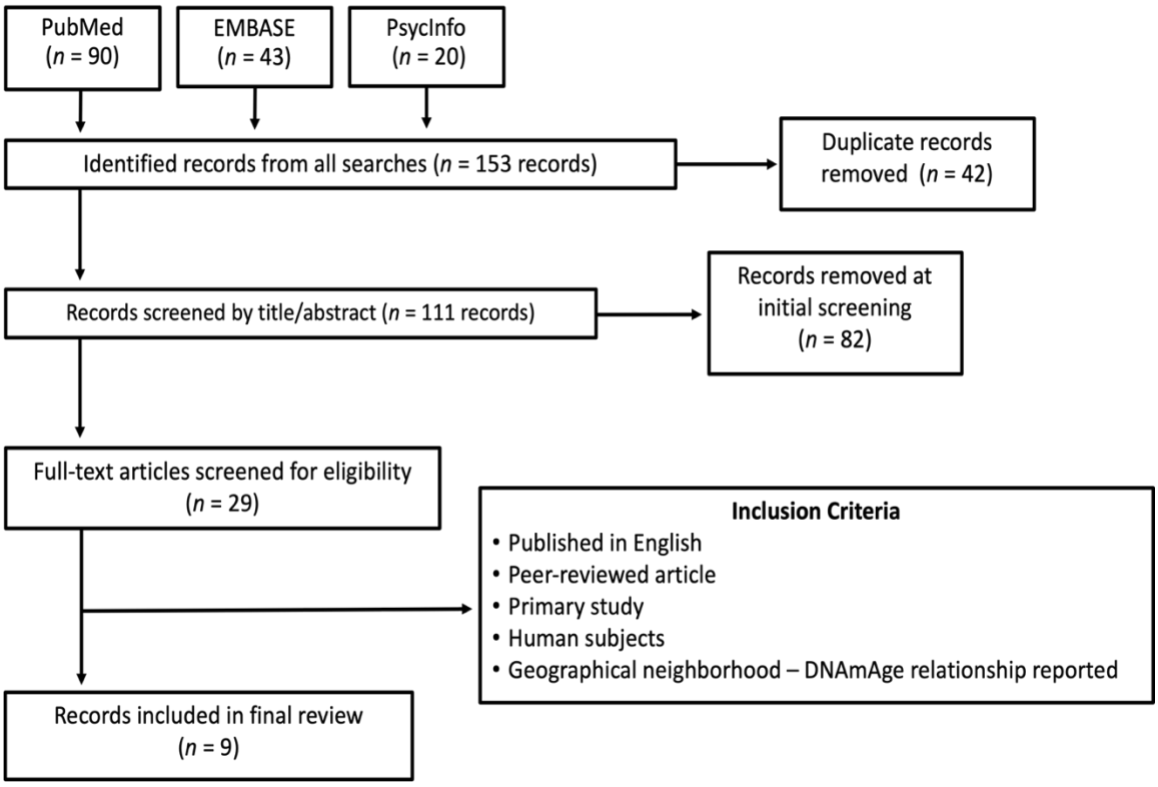
Roux, 2001). Additionally, several ways to measure epigenetic age have been developed (Bergsma & Rogaeva, 2020). A scoping review is the most suitable option when the literature to be examined is heterogeneous in nature (Peters et al., 2015). Thus, since both the neighborhood characteristics and measures of epigenetic age to be included in this review are heterogeneous in nature, a scoping review is the ideal methodology for the aims of this study.

Search Strategy and Eligibility Criteria

We completed a search of the scientific literature available in PubMed, PsycInfo, and EMBASE databases through January 16, 2022. The search strategy combined various key terms related to neighborhood-level factors and DNA methylation age: ((neighborhood OR community) AND (characteristics OR status)) AND (DNA methylation)). No time restriction was placed for the searches. However, we limited the searches to articles published in English. Studies were included if they were peer-reviewed articles, primary studies, and research focused on human subjects that addressed the relationship between a neighborhood-level environmental characteristic (physical or social) and epigenetic age. Figure 1 depicts the complete article identification process. Articles that used the term neighborhood to refer to proximity on the genome, rather than geographical residence, were excluded.

Figure 1

Study Search and Selection Process



Final eligibility was assessed for articles using the inclusion/exclusion criteria detailed above that were available in full text.

Data Extraction and Analysis

After removing duplicates, an independent abstractor reviewed the title and abstract of each article for selection. This abstractor decided whether to include or exclude each article for a full-text review. The full text was obtained and reviewed based on inclusion and exclusion criteria. Data were extracted from the eligible articles using a matrix table. Data elements included citation information, study purpose and design, sample and setting, methods, key findings, and conclusions. We added a descriptive

analysis of elements into the matrix to assess the range of neighborhood characteristics that have been studied, the nature of the relationship between those characteristics with epigenetic age, and research gaps.

Results

We obtained 153 search results. After removing duplicates and screening for eligibility based on title, abstract, and full text, we included nine articles in the final analysis (Joyce et al., 2021; Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Marini et al., 2020; Martin et al., 2021; Raffington et al., 2021; Ward-Caviness et al., 2020; Xu et al., 2021). All included articles were published between 2019 and 2021. As summarized in Table 1, most studies used a cross-sectional design, and the sample sizes ranged between 100 and 2,630 participants. Seven out of the nine studies used samples from adults (Joyce et al., 2021; Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Martin et al., 2021; Ward-Caviness et al., 2020; Xu et al., 2021), one from adolescents and children (Raffington et al., 2021), and one from children exclusively (Marini et al., 2020). Fewer than half of the studies included used multiethnic samples (Joyce et al., 2021; Martin et al., 2021; Raffington et al., 2021; Ward-Caviness et al., 2020), primarily reporting the inclusion of non-Hispanic Black and non-Hispanic White participants, with only one study reporting the inclusion of Hispanic participants (Raffington et al., 2021). A few studies used samples from only non-Hispanic Black (Lei et al., 2022; Lei et al., 2019) and non-Hispanic White (Lawrence et al., 2020; Marini et al., 2020) participants exclusively. One study (based in Australia) did not report race/ethnicity of its sample (Xu et al., 2021). All but two of the studies were conducted in the United States (Joyce et al.,

2021; Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Martin et al., 2021; Raffington et al., 2021; Ward-Caviness et al., 2020), with the others conducted in the United Kingdom (Marini et al., 2020) and Australia (Xu et al., 2021). Altogether, for the small number of studies conducted thus far, they have used a broad range of sample sizes, age ranges, and included a fair amount of diversity in ethnicity and sex but have been limited in their research design.

Table 1

General Characteristics of Reviewed Articles

Author & Year	Study Purpose	Study Design	Sample Size	Neighborhood Measurement	Epigenetic Age Calculator	Key Findings
Lei et al. (2019)	Investigate influence of neighborhood deprivation on aging in adults	CS	*N* = 100	Sum median household income, % unemployed, % below poverty line, % single-mother families, % public assistance	Ha	Neighborhood deprivation significantly positively associated with accelerated epigenetic aging
Lawrence et al. (2020)	Examine relationship between neighborhood deprivation and epigenetic age in adults	CS	*N* = 2,630	Area Deprivation Index	Ha, Ho, P, G	Residents of greatest neighborhood deprivation had greater epigenetic age acceleration in all clocks except Horvath
Marini et al. (2020)	Test hypothesis that adversity accelerates epigenetic age in children	L	*N* = 973	ALSPAC Townsend & Indices of Multiple Deprivation	Ha, Ho	Neighborhood deprivation significantly positively associated with epigenetic age acceleration using Hannum but not Horvath clock
Ward-Caviness et al. (2020)	Evaluate effect of neighborhood characteristics on	CS	*N* = 157	Trained assessors following	eMRS	Negative neighborhood characteristics (e.g., abandoned cars, alcohol

	epigenetic mortality risk score in adults			author-developed protocol of 19 indicators		advertising) associated with mortality risk. Residing in neighborhoods with below-average levels of large mature trees was also associated with mortality risk
Joyce et al. (2021)	Examine influence of neighborhood socioeconomic status on epigenetic age acceleration in adults	L	Timepoint #1: *N* = 1,036 Timepoint #2: *N* = 1,016	% With less than high school education	Ha	Decrease in neighborhood education was associated with increase in epigenetic age acceleration at 1st timepoint but not replicated at 2nd timepoint
C. L. Martin et al. (2021)	Examine association between neighborhood environment and epigenetic age in adults	CS	*N* = 158	Trained assessors following author-developed protocol of 19 indicators	Ha, Ho, P	Neighborhood environment significantly positively associated with epigenetic age acceleration using all clocks
Raffington et al. (2021)	Test hypothesis that early-life socioeconomic deprivation accelerates biological age in children and adolescents	CS	*N* = 600	Composite % unemployed, % below poverty line, % less than high school education, % single mothers, % employed in nonmanagerial position	D	Living in deprived neighborhoods associated with faster epigenetic aging

Xu et al. (2021)	Evaluate association between surrounding residential greenness and biological aging in adults	CS	*N* = 479	Normal Difference Vegetation Index & Enhanced Vegetation Index	Ha, Ho, P, G	Higher levels of surrounding residential greenness associated with lower epigenetic age acceleration using Horvath, GrimAge, and Hannum, but not PhenoAge
Lei et al. (2022)	Examine relationship between neighborhood deprivation and epigenetic age in adults	CS	*N* = 941	Area Deprivation Index	P, G, D	Neighborhood deprivation was significantly positively associated with epigenetic age acceleration using all clocks
	Study design: **CS** = cross-sectional, **L** = longitudinal. Association reported: **YES** = significant association between a neighborhood-level characteristic and EpAA reported; **NO** = no significant association reported. Epigenetic Age Calculator: **Ha** = Hannum, **Ho** = Horvath, **P** = PhenoAge, **G** = GrimAge, **D** = DunedinPoAm, **eMRS** = author developed epigenetic mortlaity risk score.					

Associations Between Neighborhood Characteristics and Epigenetic Age

Nearly all studies included in this review reported a relationship between neighborhood characteristics and epigenetic age. The only exception was a longitudinal study that reported a significant association at the first timepoint, but no significant relationship at the second timepoint 5 years later (Joyce et al., 2021). In that study, the investigators used a single indicator of neighborhood deprivation (i.e., education), which may not be as robust an indicator as multivariate measures. Thus, there appears to be a relationship between neighborhood characteristics (such as neighborhood socioeconomic status and level of residential greenness) and epigenetic age. A more thorough discussion of the measurement of neighborhood characteristics is presented below.

Did Associations Vary by Neighborhood Characteristic?

To further understand the relationship between neighborhood characteristics and epigenetic age, we examined whether this relationship depended on specific neighborhood characteristics. Overall, the studies reviewed suggest epigenetic age is associated with socioeconomic as well as physical neighborhood characteristics. In most studies, epigenetic age increased with *negative* neighborhood characteristics (neighborhood deprivation). For example, Lawrence et al. (2020) found that participants with the highest level of neighborhood deprivation (i.e., greater than the 75th percentile) had greater epigenetic age compared to participants residing in neighborhoods with the lowest level of neighborhood disadvantage (i.e., lower than the 25th percentile). Similarly, other investigators reported that *positive* neighborhood characteristics such as greenness

and the presence of large mature trees correlated with slower epigenetic aging (Martin et al., 2021; Ward-Caviness et al., 2020; Xu et al., 2021).

The quality of the study appears to affect the relationship between neighborhood characteristics and epigenetic age. Studies that robustly measured neighborhood characteristics with previously compiled information like census data (Joyce et al., 2021; Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Marini et al., 2020; Raffington et al., 2021) and those that utilized trained personnel to assess neighborhood characteristics (Martin et al., 2021; Ward-Caviness et al., 2020) found an association with epigenetic age. For example, using an index based on American Community Survey data and DNA methylation samples from a cohort of adult men and women randomly selected from neighborhoods in Iowa and Georgia, Lei et al. (2022) found an association between neighborhood deprivation and epigenetic age. Likewise, in a population-based cohort of adults from Detroit, Michigan, Martin et al. (2021) found an association between epigenetic age and neighborhood environment using trained study personnel making assessments on the ground in their participants' neighborhoods. In contrast, a study that relied on a single indicator of socioeconomic status found inconsistent associations between the level of neighborhood education and epigenetic age acceleration at different timepoints within the same cohort (Joyce et al., 2021).

Did Associations Vary by Epigenetic Clock?

There are slight differences in the number of genes in each clock, so we also investigated whether the relationship between epigenetic age and neighborhood characteristics depended on the epigenetic clock. All studies that used the Hannum clock (Joyce et al., 2021; Lawrence et al., 2020; Lei et al., 2019; Marini et al., 2020) and

GrimAge (Lawrence et al., 2020; Lei et al., 2022) reported associations with neighborhood characteristics, while three out of four studies using PhenoAge reported an association (Lawrence et al., 2020; Lei et al., 2022; Martin et al., 2021). Interestingly, in the studies reviewed that used the Horvath clock, none detected a relationship between epigenetic age and neighborhood *socioeconomic* characteristics. However, two studies found an association between epigenetic age and *physical* neighborhood characteristics when using the Horvath clock (Martin et al., 2021; Xu et al., 2021).

Regarding *intra*-study variation, four studies analyzed the relationship between epigenetic age and neighborhood socioeconomic characteristics using more than one clock (Lawrence et al., 2020; Lei et al., 2022; Marini et al., 2020; Martin et al., 2021), with one of these studies considering physical in addition to socioeconomic neighborhood characteristics (Martin et al., 2021). Two studies found consistent associations (Lei et al., 2022; Martin et al., 2021). Among non-Hispanic Black adults, Lei and colleagues (2022) found significant associations between neighborhood deprivation and epigenetic age acceleration using the PhenoAge, GrimAge, and DunedinPoAm clocks. Similarly, using the Horvath, Hannum, and PhenoAge clocks, Martin and colleagues (2021) detected a significant positive association between neighborhood poverty as well as physical neighborhood characteristics (such as the presence of graffiti, abandoned cars, and unkept roads) and epigenetic age acceleration among predominantly non-Hispanic Black adults. However, in two other studies, no association was detected using the Horvath clock (Lawrence et al., 2020; Marini et al., 2020), despite finding a significant association using Hannum (Lawrence et al., 2020; Marini et al., 2020) as well as the PhenoAge and GrimAge clocks (Lawrence et al., 2020). This inter- and intra-study

variability suggests that selection of the epigenetic clock chosen to examine the relationship between epigenetic age and neighborhood characteristics is an important consideration.

Did Associations Vary by Age, Sex, or Ethnicity?

Emerging evidence suggests that the relationship between epigenetic age and neighborhood characteristics exists in both children/adolescents and adults. Two studies in this scoping review included children or adolescents and both detected a relationship between neighborhood characteristics and epigenetic age (Marini et al., 2020; Raffington et al., 2021). Their results align with the seven studies conducted using adult participants (Joyce et al., 2021; Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Martin et al., 2021; Ward-Caviness et al., 2020; Xu et al., 2021).

Overall, studies that included all female participants found an association between some neighborhood characteristics and epigenetic age (Lawrence et al., 2020; Lei et al., 2019; Xu et al., 2021), but there was some variation based on the neighborhood characteristic and the epigenetic age calculator used. The Hannum clock was consistent across all three studies that included only female participants, irrespective of neighborhood characteristics. Two studies with all female participants used multiple epigenetic clocks (Lawrence et al., 2020; Xu et al., 2021). The findings of these two studies agreed with each other using the GrimAge clock but did not when using PhenoAge. Lawrence et al. (2020) detected a relationship between neighborhood deprivation and epigenetic age using the PhenoAge clock, while Xu at al. (2021) did not detect an association between the level of neighborhood greenness and epigenetic age. These same two studies also differed in detecting a relationship using the Horvath clock.

Specifically, Xu et al. (2021) found an association, while Lawrence et al. (2020) did not. Since no studies included in this review included all male participants, we were unable to assess for variation in association between sexes. These findings suggest that, at least for females, the association between neighborhood characteristics and epigenetic age depends on both the neighborhood characteristic being examined and the epigenetic clock used.

Studies that reported multiethnic participants were nearly unanimous in detecting an association between neighborhood characteristics and epigenetic age (Joyce et al., 2021; Martin et al., 2021; Raffington et al., 2021; Ward-Caviness et al., 2020), with the exception being a multiethnic longitudinal study that found an association at the initial timepoint but failed to replicate the association at the second timepoint (Joyce et al., 2021). Overall, the studies that used samples from all non-Hispanic Black participants (Lei et al., 2022; Lei et al., 2019) and studies that included samples from predominantly non-Hispanic White participants (Lawrence et al., 2020; Marini et al., 2020) agreed in finding a link between neighborhood characteristics and epigenetic age. However, some variation was noted based on the epigenetic age calculator used. The Hannum clock consistently detected associations across ethnicities. The studies that included samples from all non-Hispanic Black participants established a link between neighborhood characteristics and epigenetic age using multiple clocks—Hannum, PhenoAge, GrimAge, and DunedinPoAm clocks (Lei et al., 2022; Lei et al., 2019). Both studies with samples from predominantly non-Hispanic White participants found an association using Hannum, but not using the Horvath clock. There was also agreement using the PhenoAge and GrimAge clock when they were used with samples from non-Hispanic White

(Lawrence et al., 2020) and non-Hispanic Black (Lei et al., 2022) participants. These findings suggest that the relationship between epigenetic age and neighborhood characteristics holds true across different age ranges and ethnicities, further supporting the notion that associations vary depending on the epigenetic clock used.

Measurement of Neighborhood Characteristics

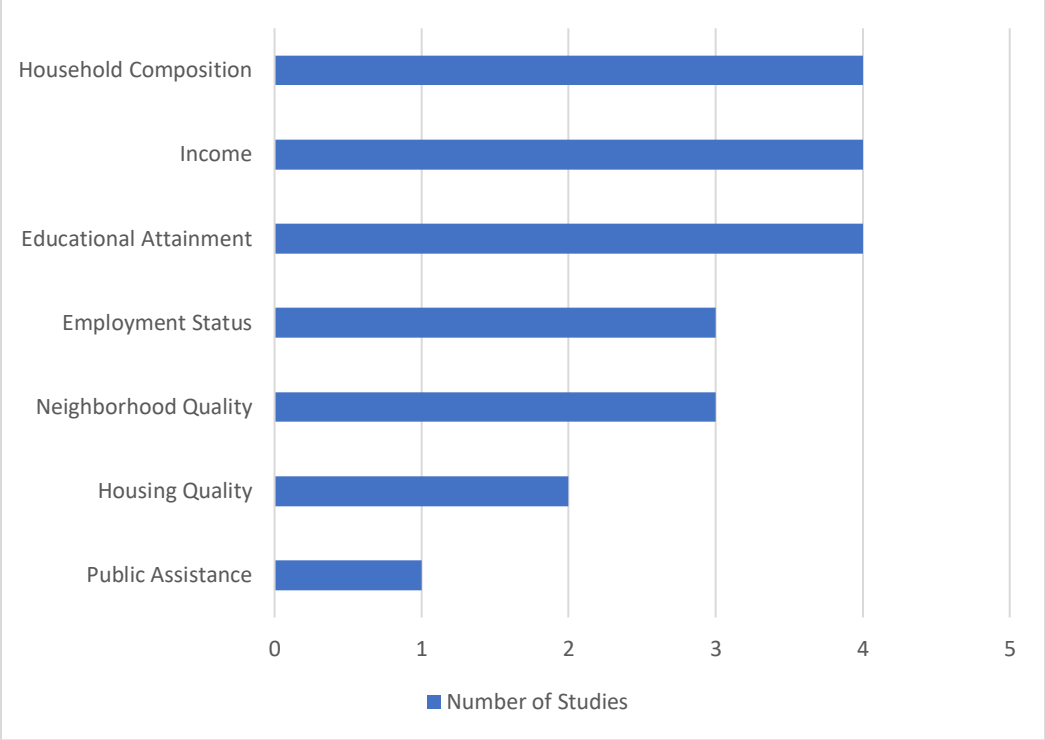
More than half of the studies included in this review examined the relationship between neighborhood socioeconomic status and epigenetic age (Joyce et al., 2021; Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Marini et al., 2020). Of these, Martin et al. (2021) and Ward-Caviness et al. (2020) included additional non-socioeconomic status indicators, considering other aspects of the neighborhood environment such as noise, the condition of sidewalks, and presence of graffiti. One study examined only one aspect of the physical environment—level of greenness (Xu et al., 2021).

Figure 2 shows categories of social and physical neighborhood characteristics reported in the articles. The most common neighborhood characteristics considered were household composition, income, and education. In most studies, neighborhoods were characterized based on attributes of the social environment using census data (Joyce et al., 2021; Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Marini et al., 2020; Raffington et al., 2021). Three studies measured physical neighborhood characteristics (Martin et al., 2021; Ward-Caviness et al., 2020; Xu et al., 2021), of which, two studies relied on a protocol in which trained personnel manually assessed neighborhood attributes such as the condition of the sidewalks, graffiti, noise, and the presence of large mature trees (Martin et al., 2021; Ward-Caviness et al., 2020). One study used satellite-

derived measurements of the level of greenness or vegetation surrounding participants' addresses (Xu et al., 2021).

Figure 2

Neighborhood-Level Variables Included in Relationship With Epigenetic Age

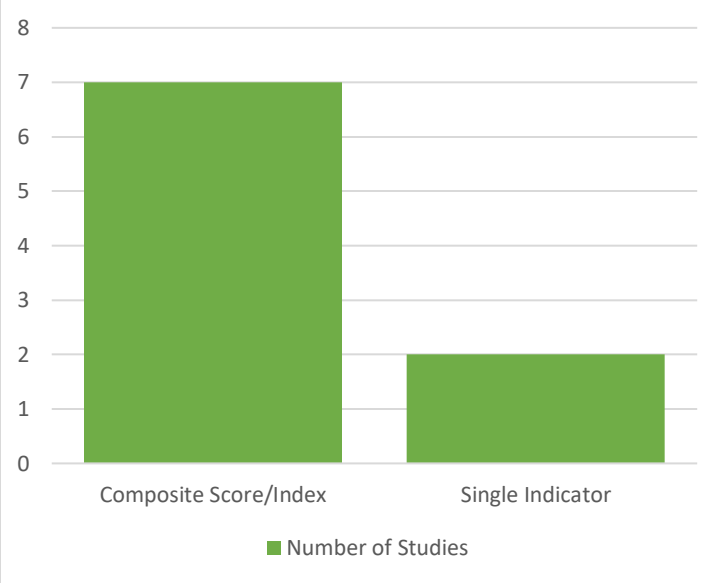


Most studies used a multivariate index, capturing several neighborhood factors within the scope of the particular neighborhood characteristic of interest. For example, in most studies of neighborhood deprivation, a multivariate index was used to assess neighborhood socioeconomic status (Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Marini et al., 2020; Martin et al., 2021; Raffington et al., 2021; Ward-Caviness et al., 2020). Likewise, for two out of the three studies measuring physical neighborhood characteristics, a multivariate index was also used (Martin et al., 2021; Ward-Caviness et

al., 2020). Of the eight studies that reported the details of their scoring, the number of neighborhood characteristics included in the multivariate indexes ranged from five (Lei et al., 2019; Raffington et al., 2021) to 19 (Martin et al., 2021; Ward-Caviness et al., 2020). Only two studies relied on a single indicator to assess neighborhood characteristics (Joyce et al., 2021; Xu et al., 2021) (Figure 3). Since multivariate indexes measure multiple aspects of a concept, these findings suggest that researchers have considered the multidimensional nature of the neighborhood environment to be of importance when investigating the relationship between epigenetic age and neighborhood characteristics.

Figure 3

Multivariate vs. Univariate Measurement of Neighborhood Characteristics



Findings were mostly consistent regardless of whether the neighborhood characteristic was measured using a multivariate index or a single indicator. All studies using a multivariate index found an association, but some variation was noted for studies

using a single indicator. Specifically, a study using a single indicator of neighborhood greenness detected an association with epigenetic age (Xu et al., 2021). However, when examining the relationship between the single indicator neighborhood education and epigenetic age longitudinally, Joyce and colleagues (2021) detected an association at the first timepoint, but not the second.

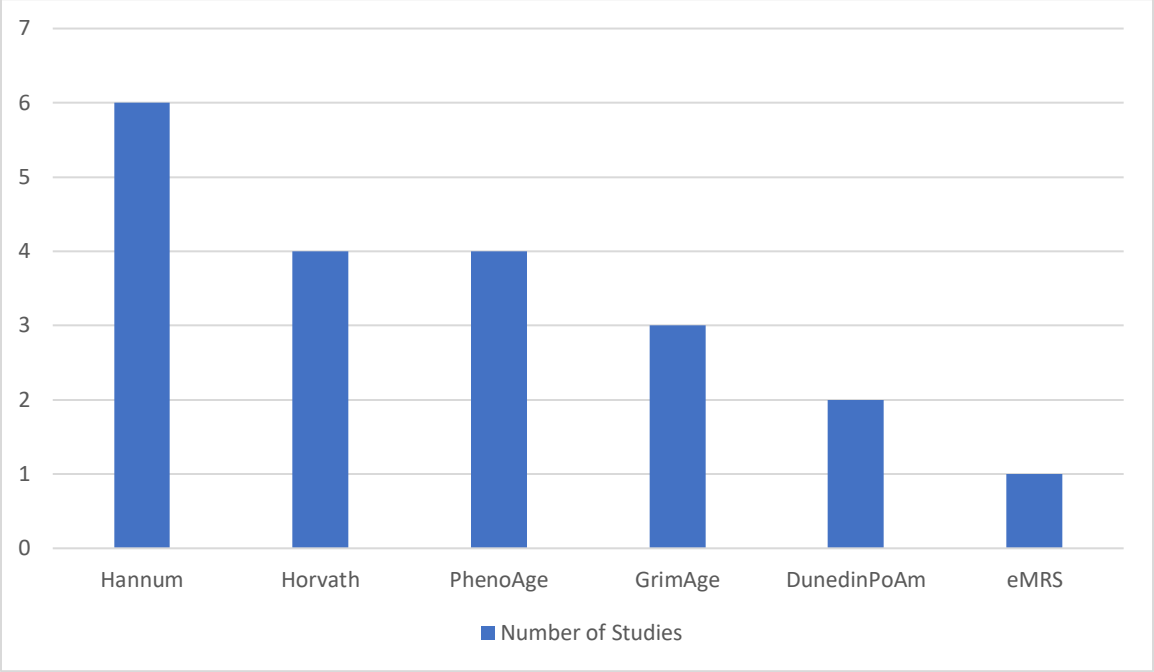
Measurement of Epigenetic Age

Six epigenetic clocks have been used to measure the relationship between neighborhood characteristics and epigenetic age, with greater reliance on the original clocks developed by Hannum et al. (2013) and Horvath (2013). As depicted in Figure 4, Hannum's clock is the most frequently used clock. Five studies assessed the relationship between epigenetic age and neighborhood characteristics using multiple clocks (Lawrence et al., 2020; Lei et al., 2022; Marini et al., 2020; Martin et al., 2021; Xu et al., 2021). Four studies used a single epigenetic age calculator (Joyce et al., 2021; Lei et al., 2019; Raffington et al., 2021; Ward-Caviness et al., 2020). Of the four studies, one used an author-developed method to assess mortality risk based on DNA methylation (Ward-Caviness et al., 2020) rather than an epigenetic clock previously described in the literature.

There has been less variation in the type of samples collected for DNA, with all studies reviewed relying on a single tissue type for its DNA source. Some DNA methylation changes associated with aging are tissue-specific (Koch & Wagner, 2011). So, the type of sample used for DNA extraction for subsequent epigenetic age calculation is a necessary consideration. Most studies in this review used blood samples (Joyce et al., 2021; Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Marini et al., 2020; Martin

Figure 4

Distribution of Epigenetic Clocks



et al., 2021; Ward-Caviness et al., 2020; Xu et al., 2021). The one exception used saliva (i.e., primarily epithelial cells) (Raffington et al., 2021). The variety of clocks used suggests that there is as yet no gold standard for epigenetic age calculation, and the variation in findings depending on the clock that was used supports this notion.

Identified Gaps

The literature reviewed revealed that few studies have explored a relationship between epigenetic age and physical neighborhood characteristics. Neighborhood socioeconomic status was the predominant neighborhood characteristic examined (Joyce et al., 2021; Lawrence et al., 2020; Lei et al., 2022; Lei et al., 2019; Marini et al., 2020; Martin et al., 2021; Raffington et al., 2021; Ward-Caviness et al., 2020). Exceptions included one study that examined epigenetic age with the level of residential greenness

(Xu et al., 2021) and two studies that included neighborhood socioeconomic status along with physical aspects of the neighborhood environment (Martin et al., 2021; Ward-Caviness et al., 2020). Another gap in the literature is the lack of Hispanic participants. Only one study included Hispanic participants (Raffington et al., 2021), with most relying on samples collected from non-Hispanic White or non-Hispanic Black participants. Finally, only two studies utilized a longitudinal design (Joyce et al., 2021; Marini et al., 2020), so more studies are needed that investigate the potential effects of long-term exposures to neighborhood characteristics.

Discussion

The purpose of this review was to examine the literature on the relationship between neighborhood characteristics and epigenetic age, describe how studies of this relationship have measured neighborhood characteristics and epigenetic age, and identify gaps in the current research. The neighborhood environment has been associated with many age-related conditions, and this review suggests a nascent but growing body of evidence of the relationship between neighborhood characteristics and epigenetic age. We identified three main findings relating to epigenetic age and neighborhood characteristics. First, current evidence supports the assertion that neighborhood characteristics are significantly associated with epigenetic age. Specifically, negative neighborhood characteristics (neighborhood deprivation) correlate with older epigenetic age. These results are consistent with previous studies linking older epigenetic age with age-related health conditions and all-cause mortality (Hillary et al., 2020; Marioni et al., 2015; Perna et al., 2016; Zhang et al., 2017). The relationship between neighborhood

characteristics and epigenetic age suggests that neighborhood characteristics may induce epigenetic changes that correlate with accelerated aging and age-related health conditions, providing a potential biological mechanism for this phenomenon.

A second major finding of this review is that various neighborhood characteristics are associated with different epigenetic clocks. For example, a significant association was found between neighborhood deprivation and epigenetic age acceleration using the Hannum clock (Lawrence et al., 2020; Lei et al., 2019), but not using the Horvath clock (Lawrence et al., 2020; Marini et al., 2020). However, a significant association *was* found using the Horvath clock in the relationship between a physical neighborhood characteristic (greenness) and epigenetic age acceleration (Xu et al., 2021). The variability in findings suggests that the ability to detect an association between neighborhood characteristics and epigenetic age may be influenced by neighborhood characteristics, epigenetic calculator, and the interaction of both. There is no gold standard measure of epigenetic age, and there is still a need to fully discern how environmental factors impact epigenetic age (Bell et al., 2019). Epigenetic clocks have most often been constructed using machine learning to identify a parsimonious number at which DNA methylation of those CpG sites will correlate with chronological age (Bell et al., 2019). As a result of this process: (a) the number of CpG sites used in the epigenetic age calculation are greatly reduced from the total number of CpG sites in the genome, and (b) the specific CpG sites chosen for each clock differ. Indeed, there is not much overlap in the CpG sites used in different epigenetic clocks (Liu et al., 2020). Furthermore, DNA methylation changes vary based on the particular environmental exposure (Dhingra et al., 2018; Martin & Fry, 2018). In this way, the influence of specific

neighborhood characteristics on epigenetic age may be revealed by one clock but not another, and a specific clock may pick up some neighborhood characteristics but not others. The variability of findings in this review suggests this is the case.

Finally, we found many gaps in the literature regarding the types of neighborhood characteristics used in relation to epigenetic age. Several features of the physical environment have been linked to age-related disease outcomes. For example, exposure to air particulate matter, residential noise, and pollutants correlates with an increased risk for type 2 diabetes (Beulens et al., 2022). Similarly, worse cardiovascular disease outcomes, including increased hospitalizations and cardiovascular disease-related mortality, have been associated with air pollution (Brook et al., 2004), while noise has been associated with hypertension and stroke (Münzel et al., 2014). Also, aspects of the neighborhood-built environment like walkability and access to healthy food have been linked to cardiovascular disease outcomes (Malambo et al., 2016). However, these neighborhood characteristics in relationship with epigenetic age do not appear to have been examined thus far. For most studies in this review, the authors focused on neighborhood socioeconomic factors and relied heavily on census-based measures. Diez-Roux and Mair's (2010) seminal work on the effects of the neighborhood on health recognized that most early studies involved predominantly socioeconomic and census-based measures of the neighborhood. Since then, researchers have collected additional measures of the neighborhood environment to understand neighborhood effects on health behaviors and outcomes such as obesity and hypertension (Diez Roux & Mair, 2010). Interestingly, our review reveals a similar evolution of the body of research about neighborhood and epigenetic age.

While the research is still in its infancy, and this review cannot speak to causality in the relationships examined, future research is promising in its potential to one day help explain neighborhood disparities in health. More well-designed studies are needed to explore the full range of neighborhood characteristics that may be impacting the pace of epigenetic aging.

Strengths and Limitations

This review has some strengths and limitations that must be considered when utilizing the results. First, to our knowledge, this is the first scoping review examining the relationship between various aspects of neighborhood characteristics, beyond socioeconomic status, and epigenetic age. Second, the use of the scoping review methodology is another strength. Scoping reviews allow for exploration of an area of research that is broad and/or still emerging (Lockwood et al., 2019). Considering the small number of studies conducted thus far, covering a wide range of possible neighborhood characteristics, and using multiple epigenetic clocks, this approach was a good fit to answer the research questions.

Despite the above-mentioned strengths, our review has some limitations. Though the entire team reviewed the results, one abstractor performed data extraction. Second, we focused primarily on articles published in the English language. Thus, it is possible that we missed unpublished studies and studies published in other languages. Also, while a scoping review was the most appropriate approach to address the study's aims, the methodology has downsides. The nature of taking a broad perspective on the data belies the ability to do a meta-analysis of the data that are extracted (Tricco et al., 2016). Additionally, scoping reviews can be useful for the determination of the need for a

subsequent systematic review (Lockwood et al., 2019). However, the studies selected for review intentionally included multiple measures of neighborhood characteristics and epigenetic age. So, evaluating the suitability for a systematic review was not an aim of this study and was not addressed.

Conclusion

Neighborhoods do impact health outcomes and the development of age-related diseases, but no review had yet reported the breadth of neighborhood characteristics that are associated with epigenetic age—a biomarker strongly correlated with age-related diseases. This review mapped the existing literature on the relationship between neighborhood characteristics and epigenetic age and, overall, found support for a connection. The findings suggest that variations in neighborhood characteristics are associated with different epigenetic clocks, including aspects of both the socioeconomic and physical environment. This review enhances our understanding of the importance of neighborhood characteristics for future work on the effects of the neighborhood on epigenetic aging, morbidity, and mortality.

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THE AREA DEPRIVATION INDEX CORRESPONDS EFFECTIVELY WITH OTHER MEASURES OF OBJECTIVE SOCIOECONOMIC STATUS IN ADULTS WITH CHRONIC LOW BACK PAIN

by

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THE AREA DEPRIVATION INDEX CORRESPONDS EFFECTIVELY WITH OTHER MEASURES OF OBJECTIVE SOCIOECONOMIC STATUS IN ADULTS WITH CHRONIC LOW BACK PAIN

Chronic pain has been recognized as a significant cause of suffering in the world (International Association for the Study of Pain, 2017), with an estimated 11% of American adults experiencing pain every day and an annual economic cost approaching $635 billion (National Center for Complementary and Integrative Health, 2018). Chronic pain is a major cause of disability (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011), negatively affecting a person's quality of life and daily activities of work and family (Dueñas et al., 2016). Low back pain is one of the most common painful conditions and is the leading cause of disability worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). It is consistently among the top 5 reasons for healthcare visits (Ferreira et al., 2010; Maher et al., 2017). Although many individuals with acute low back pain recover, about 1 in 5 progress to chronic low back pain (cLBP), lasting more than 3 months (Maher et al., 2017). The societal cost of cLBP is very high (Dutmer et al., 2019); it is associated with decreased quality of life (Husky et al., 2018), depressive symptoms (Pinheiro et al., 2016; Robertson et al., 2017), and decreased work productivity (Amirdelfan et al., 2018; Dutmer et al., 2019; Vlaeyen et al., 2018). To date, cLBP remains a major public health problem despite concerted efforts to address it.

Prior studies have documented the relationship between socioeconomic status (SES) and pain outcomes (Dorner et al., 2011; Dorner et al., 2018; Ikeda et al., 2019; Morgan et al., 2011; Riskowski, 2014; van Hecke et al., 2013). Generally, lower SES has been associated with virtually every aspect of poor chronic pain outcomes, including pain

severity (Morgan et al., 2011), pain interference (Dorner et al., 2011), and decreased quality of life (Mielck et al., 2014). This trend towards worser pain outcomes in chronic pain has also been documented in cLBP (Hartvigsen et al., 2018; Jonsdottir et al., 2019 & Ikeda et al., 2019). Specifically, higher rates of cLBP correlate with low SES and low educational attainment (Jonsdottir et al., 2019; Ikeda et al., 2019).

Investigators frequently use demographic variables to define SES, but the operational measurement of SES varies between studies. Individual level SES has been operationalized using objective and subjective factors (Jackman & Jackman, 1973). Frequently used objective measures of SES include education, income, occupation, and wealth. Research suggests that an individuals' highest attained level of education is associated with income, wealth, living conditions, and health outcomes (Galobardes et al., 2007). Subjective social status (SSS) is the internally derived perception of one's position in society (Jackman & Jackman, 1973) and predicts various health outcomes after accounting for objective measures of SES. However, it has been suggested that SSS may differ by sex, race, and ethnicity (Shaked et al., 2016; Wolff et al., 2010). Subjective social status is frequently measured using the MacArthur Scale of Subjective Social Status (or MacArthur Ladder) (Ferreira et al., 2018; Hoebel et al., 2017; Stanford University Department of Psychology, n.d.; Subramanyam et al., 2012; Zell et al., 2018). Prior work from our group shows that lower SSS correlates with more severe cLBP and increased pain interference (Aroke et al., 2020).

Besides personal (objective and subjective) measures of SES, the SES of an individuals' environment also affect their living conditions and health (Ross & Mirowsky, 2008). Living in disadvantaged neighborhoods has been associated with poor

health outcomes, including cardiovascular disease, obesity, diabetes, and chronic pain (Barber et al., 2016; Brennan & Turrell, 2012; Ulirsch et al., 2014). The Area Deprivation Index (ADI) is a well-validated instrument that measures neighborhood socioeconomic status (SES). Prior studies have used the ADI to examine the effects of neighborhood SES on several health outcomes (Chamberlain et al., 2020; Durfey et al., 2019; Kind et al., 2014; Kurani et al., 2020; Oates et al., 2019). For example, low neighborhood SES has been found to be associated with multimorbidity of chronic diseases (Chamberlain et al., 2020), diabetes and blood pressure control (Durfey et al., 2019), and the presence of methicillin-resistant *Staphylococcus aureus* in pediatric patients with cystic fibrosis (Oates et al., 2019). The ADI assesses SES by measuring social deprivation and neighborhood disadvantage (Kind & Buckingham, 2018). Of relevance to this study, emerging evidence suggests that the SES of the neighborhood in which a person lives (i.e., the level of neighborhood disadvantage) is an important factor in pain outcomes (Green & Hart-Johnson, 2012; Maly & Vallerand, 2018). However, little is known about the utility of various measures of SES to assess the association of SES on chronic pain outcomes. While measures of SES are meant to measure the same overarching concept, they may not be interchangeable. The specific measure chosen to examine relationships between SES and back pain outcomes may influence its predictive ability (Fliesser et al., 2017). Informed by the social determinants of health, this paper will generally examine which measure of SES better predicts cLBP outcomes. The purpose of this study was to compare the ADI with other measures of SES in predicting pain severity and interference in adults with cLBP.

Background and Conceptual Framework

An individual's SES is an essential factor for understanding the personal and societal impact of chronic pain. Chronic pain occurrence and severity increases as objective measures of SES decreases (van Hecke et al., 2013). Other investigators have reported that low SES is linked to poor pain outcomes, while high SES is associated with better results in various pain conditions, including back pain (Dorner et al., 2011; Dorner et al., 2018; Grol-Prokopczyk, 2017; Gurung et al., 2015; Hoy et al., 2010; Janevic et al., 2017; Yu et al., 2020).

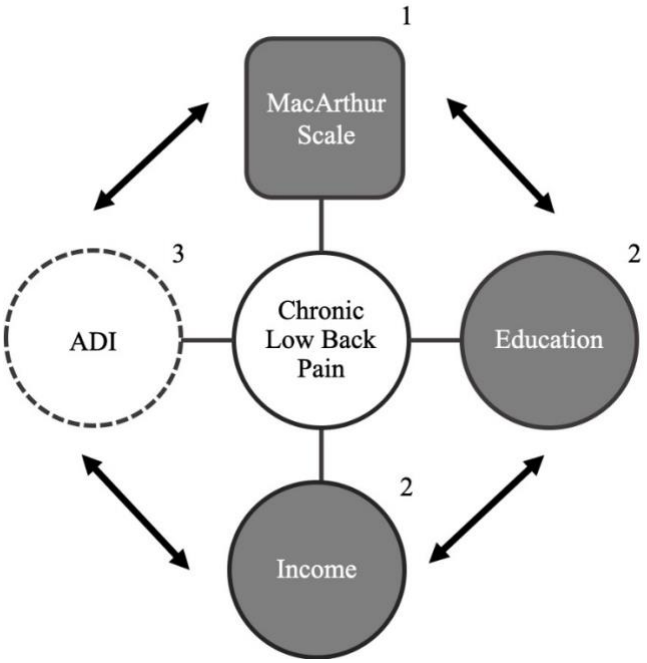
In 2010, the World Health Organization published the social determinants of health (SDOH) framework that systematically maps out determinants of health to structural intermediary and health system levels (Solar & Irwin, 2010). SDOH include the conditions in which people live, work, play, and grow. Many SDOH factors tend to cluster among individuals living in underprivileged circumstances and tend to interact with each other. As such, personal factors influence an individual's health and the environment. In turn, their environment affects both personal factors (e.g., health behaviors) and health outcomes (Artiga & Hinton, 2018). The SDOH framework has been used to explore how various chronic conditions are affected by social (personal and environmental) factors. For instance, in 2000, hundreds of thousands of deaths were attributable to negative SDOH, including low education, individual-level poverty, and area-level poverty (Galea et al., 2011).

As depicted in Figure 1, an individual's SES (objective and subjective measures of SES) influences cLBP outcomes. Conceptually, objective measures of SES include individual (income and education) and environmental (ADI) factors (Galobardes et al.,

2007; Krieger et al., 1997; Ross & Mirowsky, 2008; Singh, 2003). These objective measures of SES influence and are influenced by SSS (MacArthur's social status ladder).

Figure 1

Relationship of Objective and Subjective SES Measures and Chronic Low Back Pain



Note. ADI = Area Deprivation Index; 1= Individual-Level, Subjective; 2=Individual-Level, Objective; 3=Area-Level, Objective.

Methods

Study Design and Participants

This methodological study employed a secondary analysis of data collected for an ongoing study: Examining Racial and Socio-economic Disparities in Chronic Low Back Pain (ERASED) (R01MD010441). The goal of the ERASED study is to characterize racial differences in cLBP outcomes using a socio-economic framework. Details of the

ERASED study have previously been published (Aroke et al., 2020; Penn et al., 2020). Briefly, adults between the ages of 19 and 85 years were recruited. Respondents were included if they had non-specific low back pain lasting more than 12 weeks. Exclusion criteria included the presence of other conditions that may confound result interpretation, such as pain conditions (e.g., ankylosing spondylitis, cancer pain, fibromyalgia), neurological diseases (e.g., Parkinson's, epilepsy), or medical conditions (e.g., uncontrolled hypertension or poorly controlled diabetes). Participants included in the current study were recruited between November 2017 and November 2019. Only participants with data for all four measures (ADI, income, education and SSS) of SES being examined in this study were included for analysis. The Institutional Review Board at the University of Alabama at Birmingham reviewed and approved the ERASED study. All procedures were carried out following guidelines for the ethical conduct of research.

Measures

Demographic data included age, sex (male vs. female), and self-identified race (Non-Hispanic Black, Non-Hispanic White, and other). Measures were chosen to represent both area-level and individual SES, as well as objective and subjective SES. The goal was to capture a broad range of aspects of SES with which to compare the ADI. Income and education - measured as self-reported annual household income after taxes and the highest level of education, respectively - served as objective measures of SES at the individual level. Several valid and reliable instruments were used to assess neighborhood disadvantage, SSS, pain severity, and pain interference – the ADI,

MacArthur Ladder of Subjective Social Status, and Brief Pain Inventory (BPI) respectively.

Area Deprivation Index

The ADI is a validated objective measure of SES at the area-level, using neighborhood disadvantage (Singh, 2003; Kind & Buckingham, 2018). Each participant's address was linked to its respective census block, which is publicly available data. The ADI score is created using 17 census indicators of SES using domains such as income, housing, employment, and education (Kind & Buckingham, 2018; Kind et al., 2014). For each participants' census block, we used the 2015 ADI v.2.0 (available at www.neighborhoodatlas.medicine.wisc.edu) that assigns a decile (i.e., 1-10) ADI score at the state level. For analysis, the Alabama state-level ADI decile scores were stratified into quintile rankings (i.e., 1-5), whereby the highest ranking '5' represented the greatest level of neighborhood disadvantage and '1' represented the lowest level of neighborhood disadvantage. The ADI has demonstrated high internal consistency (i.e., Cronbach's alpha 0.94) (Singh, 2003; Singh et al., 2002; Singh & Siahpush, 2002) and a high test-retest reliability of 0.89 (Singh et al., 2002)

MacArthur Ladder of Subjective Social Status

The MacArthur ladder is a commonly used instrument that measures SSS at the individual level using a visual analog of a ladder (Adler & Stewart, 2007). Participants compare their self-perceived social status relative to others based on the following instructions:

> Think of this ladder as representing where people stand in the United States. At the top of the ladder are the people who are the best off – those who have the most money, the most education and the most respected jobs. At the bottom are the people who are the worst off – who have the least money, least education, and the least respected jobs, or no job. The higher up you are on the ladder, the closer you are to people at the very top; the lower you are, the closer you are to the people at the very bottom. Please place a large "X" on the rung of the ladder for where you think you stand at this time in your life, relative to other people in the United States.

Participants ranked their position on the rungs of the ladder 0-10 corresponding with their subjective impression of their level of social status. The MacArthur ladder is a widely used instrument and has been translated into many languages (Ferreira et al., 2018). It has a moderate test-retest reliability ($\rho = 0.62$) (Operario et al., 2004), face validity, moderate concurrent validity (Kappa = 0.55-0.67) (Ferreira et al., 2018) and strong construct validity (Cundiff et al., 2013).

Brief Pain Inventory – Short Form

The BPI is a valid and reliable self-administered 11-item questionnaire to assess clinical pain with an internal consistency reliability of greater than 0.85 (Song et al., 2016; Tan et al., 2004; Ferreira et al., 2018; Majedi et al., 2017; Tan et al., 2004). It measures two dimensions of pain: pain severity (intensity) and pain interference. The construct validity has previously been reported using factor analysis (Ferreira et al., 2011; Song et al., 2016; Tan et al., 2004). Prior work by our team indicates that BPI has internal

consistency $\alpha = 0.94$ in our sample (Aroke et al., 2020). Participants were asked to rate their pain at its worst, least, and average for the last 24 hours and at the time of the study at a scale from 0 to 10. The mean of these 4 -items correspond to the BPI-pain severity score. Using the same type of 0 to 10 scales, participants rated separately how their pain interferes with their life in the following 7 domains: 1) mood, 2) relations with other people, 3) enjoyment, 4) ability to concentrate, 5) appetite, 6) general activity, and 7) walking. Both pain severity and interference items are scored from 0-10.

Data Analysis

The ADI and other measures of SES were compared using Spearman correlations, coefficient of multiple determination partial R^2, and goodness-of-fit tests Akaike information criterion (AIC) and Bayesian information criteria (BIC). The strength of the correlation coefficients was classified as follows: negligible ($\rho < 0.10$), weak (0.10 - 0.39), moderate (0.40 - 0.69), strong (0.70 - 0.89), and very strong (0.90 - 1.00) (Schober et al., 2018). Linear regression modeling was used to determine the relative contributions of ADI, income, education, and SSS to pain severity/interference. For comparison, partial R^2 of 0.02-0.14 were considered as small, 0.15-0.34 as medium, and 0.35 or greater as large (Cohen, 1992). Also, lower AIC/BIC scores were considered better, and an internal consistency Cronbach's $\alpha = 0.7$-0.95 was considered acceptable (Tavakol & Dennick, 2011). Test-retest reliability of the ADI was assessed using a Bland-Altman plot. A power analysis using G*Power 3.1 showed that a sample size of 104 eligible was sufficient to detect a weak correlation ($\rho = 0.27$) and a ΔR^2 of 0.08 with 80% statistical

power and alpha level of 0.05 (Faul et al., 2009). Data were analyzed using R version 4.0.2 statistical software.

Results

Pain severity and interference data were available for 129 participants. Of these, data for all variables of interest were available for 104 participants with cLBP, who were included in the final analyses. Participants were on average, 45 years old and tended to be women (58.7%), and African American (56.7%). The median household income was $35K–39.9K, falling below the Alabama State median income ($48K) and national median income level ($60K) (www.census.gov/quickfacts). Approximately 74% of participants received some college education, graduated from college or attended graduate school. On average, participants rated their social status as 5.1 (SD = ±2.0) out of 10. ADI scores were available for 97% of participants representing 85 census block groups, across five counties (Jefferson, Shelby, Bibb, Walker, and Winston) in Central Alabama. Table 1 summarizes the characteristics of participants included in the study.

Correlations of Objective and SSS

As depicted in Table 2, there was a statistically significant moderate negative relationship between the objective measures of social status (income and education) and the ADI, ρ = -0.57 and -0.45, respectively. However, ADI and SSS were not significantly correlated ($p = 0.335$). In

Table 1

Characteristics of Participants (N = 104)

Characteristic	Mean (SD) or % (n)
Age in years	45 ± 13
Sex	
Female	58.7% (61)
Male	41.3% (43)
Ethnicity	
African American	56.7% (59)
Caucasian	41.3% (43)
Unknown	1.9% (2)
Area Deprivation Index (1-5)	2.7 (1.5)
Income (Median)	$35K – $39.9K
Education	
Partial High School	3.8% (4)
High School Graduate	22.1% (23)
Partial College	31.7% (33)
College Graduate	24% (25)
Graduate/Professional School	18.2% (19)

addition, both pain severity and pain interference negatively correlated with individual measures of social status and positively correlated with ADI. In contrary, the relationship between SSS and pain severity was not statistically significant ($p = 0.11$). Similarly, the

relationship between pain interference and both education and SSS were not statistically significant.

Table 2

Spearman Correlations Between Measures

	1.	2.	3.	4.	5.	6.
1. ADI	-					
2. Income	-0.566**	-				
3. Education	-0.449**	0.455**	-			
4. SSS	-0.096	0.311**	0.181	-		
5. Pain Severity	0.396**	-0.507**	-0.271*	-0.16	-	
6. Pain Interference	0.33**	-0.428**	-0.102	-0.152	0.627**	-

*p<0.05. **p≤0.001.

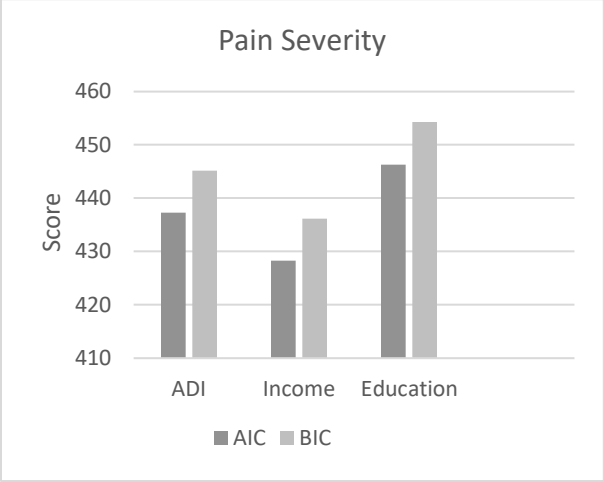
Note. ADI=Area Deprivation Index. SSS=Subjective Social Status.

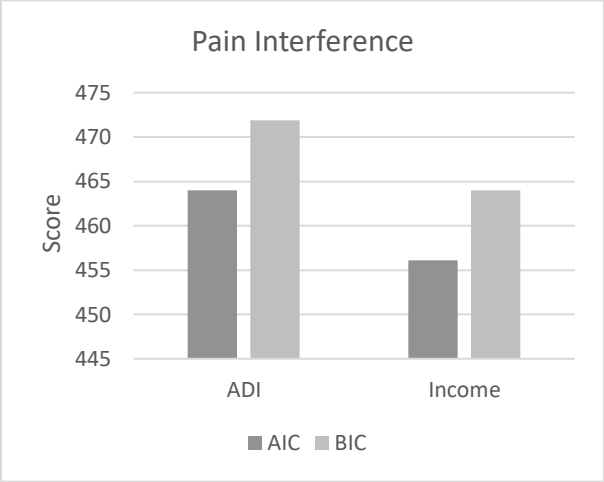
Comparing Predictors of Pain Severity and Interference

The average pain severity and interference scores were 5.1 (SD ± 2.1) and 4.1 (SD ± 2.3), respectively. The objective measures that showed significant correlations with pain outcomes were fitted into different linear models to compare their ability to predict pain severity/interference (Figure 2). For pain severity, the model's goodness-of-fit AIC and BIC suggested that income outperforms other measures of objective SES (AIC = 428.29/BIC = 436.22), followed by ADI (AIC = 437.24/BIC = 445.17), with education performing least well (AIC = 446.35/BIC = 454.29). Likewise, for pain interference, AIC and BIC suggested that income performs best (AIC = 456.08/BIC = 464.01), followed closely by ADI (AIC =4 63.96/BIC = 471.90).

Figure 2

AIC and BIC Scores for SES Pain Severity and Pain Interference With SES Measures





Assessment of Independent Contribution to Pain Outcomes

We fitted each objective measure of SES into a multiple regression model to assess its independent contribution to pain outcomes assessed. Results of the model predicting pain severity indicated that income made the largest contribution (partial R^2 = 0.098), followed by ADI (partial R^2 = 0.021). Similar results were obtained from the model predicting pain interference. The model revealed that while the ADI (partial R^2 =

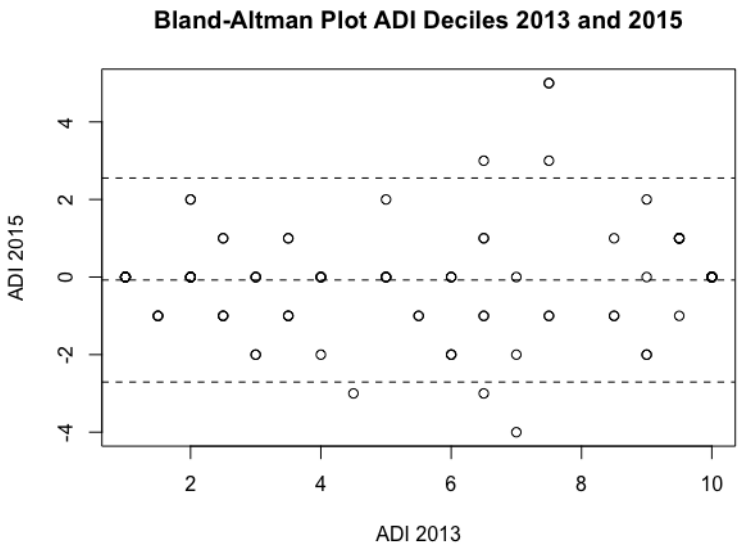
0.029) makes a small independent contribution, the contribution of income (partial R^2 = 0.100) was greatest. Education contributed a small amount to the interference model (partial R^2 = 0.026) and an insignificant amount to the pain severity model (partial R^2 = 0.0003).

Reliability of ADI and BPI

We used ADI decile scores from 2013 and 2015 to determine its test-retest reliability. The test-retest reliability of the ADI was excellent with an intraclass correlation of 0.92 ($p < 0.001$; 95% CI: 0.89 – 0.94). Figure 3 displays the Bland-Altman plot for the differences between the 2013 and 2015 ADI decile scores. Most differences were clustered within two deciles, which are acceptable limits of agreement (Polit & Beck, 2017). Internal consistency of the BPI in our sample was high with a Cronbach's alpha of 0.95 (95% CI: 0.93 – 0.96).

Figure 3

Degree of Agreement Between ADI Deciles for 2013 and 2015



Note. ADI = Area Deprivation Index.

Discussion

Our study offers preliminary evidence that the ADI is an effective measure of SES and adds to the growing body of literature indicating neighborhood disadvantage is an important predictor of pain outcomes. In direct comparisons between objective and subjective measures of SES, our results showed that income performed best at predicting pain severity and interference. However, the ADI outperformed education and SSS, which are other more well-established measures of SES (Galobardes et al., 2007; Krieger et al., 1997; Singh-Manoux et al., 2005). Our findings are consistent with prior studies, which found lower neighborhood SES is associated with poorer pain outcomes. Living in a disadvantaged neighborhood is associated with increased musculoskeletal pain and increased pain interference with daily activities following motor vehicle accident (Ulirsch

et al., 2014). Similarly, greater non-inflammatory musculoskeletal pain interference has been reported among individuals living in low SES neighborhoods in Norway (Brekke et al., 2002). Likewise, Fuentes et al. (2007) found that *high* neighborhood SES is associated with *lower* chronic pain in adults over age 50 years. However, other investigators have shown that while low neighborhood SES is associated with new-onset chronic widespread pain, that relationship is not robust and does not hold up once psychological comorbidities are considered (Davies et al., 2009). This discrepancy may be related to the fact that the neighborhood SES measure used by Davies and colleagues (2009) did not account for income and poverty, which contribute to ADI scores. To our knowledge, this is the first study to offer evidence that suggest that neighborhood disadvantage correlates with pain severity and pain interference in *cLBP*. Thus, for adults with cLBP, ADI may be a good predictor of pain outcomes.

Area-Level Versus Individual-Level Measures of SES

Our findings suggest that there is a moderate relationship between individual-level versus area-level measures of SES. Also, the area-level measure of SES (i.e., ADI) performs better than some individual-level measures of SES in predicting pain severity and pain interference. The strength of the relationship in our study is slightly higher than previously reported. Buajitti and colleagues (2020) reported a low correlation between individual and area-level SES among participants in the population-based Canadian Community Health Survey. Diez-Roux et al. (2001) found weak correlations between individual and area-level measures of income in an examination of three U.S. based cohorts. The differences in the strength of the relationship between individual and area-

level measures may be related to the fact that various measures capture different dimensions of SES. Also, it may reflect the relative homogeneity of ADI in our study sample.

While the relationships between ADI and income, as well as the ADI and education were significant, the relationship between the ADI and SSS were not. Thus, supporting the view that area- and individual-level measures of SES are related and multidimensional, but not interchangeable (Galobardes et al., 2007; Krieger et al., 1997; & Geyer et al., 2006). It is possible that an individual's neighborhood may be a reflection of their income and education, which does not necessarily reflect the individual's perception of their SES. Unfortunately, this complex relationship is under-explored among individuals living with cLBP. Fliesser and colleagues (2017), examined the relationship of chronic back pain outcomes with three different singular, individual-level measures of SES and a multidimensional, individual-level index. While the multidimensional measure predicted pain intensity best, singular measures were better at predicting disability. They concluded that the predictive ability of SES on back pain is variable based on the SES measure that is chosen (Fliesser et al., 2017). Other investigators have argued that it may not be "useful or theoretically compelling to search for a single 'best' indicator" of SES because different measures of SES capture different dimensions of the social hierarchy (Galobardes et al., 2007). Therefore, different SES indicators may measure different ways SES impacts health (Galobardes et al., 2007). Ultimately, our results support the inclusion of area-level indicators *in addition* to individual-level measures to better understand the impact of SES on cLBP.

Objective Versus Subjective Measures of SES

In our study, objective measures of SES significantly predicted pain severity and interference, while our subjective SES measure did not. These findings support the fact that objective and subjective measures of SES are not interchangeable (Shaked et al., 2016). Other studies have reported that objective measures of SES are associated with back pain outcomes. Using the objective measures income and education, Dorner et al. (2011) found lower SES to be associated with greater disability from pain. Similarly, a review by Hoy et al. (2010) found that low educational status is a common risk factor for low back pain. Jonsdottir et al. (2019) report an association between low SES and low educational attainment as risk factors for chronic back pain. Similarly, in her study using nationally representative data from the U.S., Riskowski (2014) found increased odds of back pain for both men and women with the lowest SES.

Limitations

This study has a number of limitations, including the modest number of participants, homogeneity of participants neighborhood, and idiosyncratic relationship between predictors and pain outcomes. Due to missing data on full address and income, approximately 80% of the original 129 participants were included in the final analysis. While there is no set cutoff for missing data, five percent is considered inconsequential and over ten percent may be considered problematic for inference (Dong & Peng, 2013). Also, most of our participants resided in the Birmingham-Hoover, Alabama metropolitan area. The Birmingham-Hoover metropolitan area covers over 5200 square miles and is the most populous area of the state of Alabama, with an estimated population of over 1.1

million (U.S. Census Bureau, 2018). Future studies should include participants from other geographic areas because measuring SES involves assessment of a social hierarchy, which may vary from one geographic location to another (Jackman & Jackman, 1973; Singh-Manoux et al., 2005). The use of the ADI that relies on census block data is a major limitation. This is because the reliability of the ADI score depends on the accuracy of the census data (Messer & Kaufman, 2006). However, multiple indicators are preferred when measuring SES (Messer & Kaufman, 2006). Thus, the breadth of the census data could be a strength because the ADI uses 17 indicators to assess neighborhood SES. Finally, the cross-sectional approach limited our ability to determine how long the participants had lived in the disadvantaged neighborhood.

Relevance to Nursing Practice and Research

Our findings have important implications for nursing practice and research. These findings suggest that research on SES and pain that encompasses both area-level and individual-level factors will provide valuable perspective on pain outcomes. Considering that SES may play a role in the development of pain and musculoskeletal pain severity (Maly & Vallerand, 2018; Riskowski, 2014), our findings support the adoption of neighborhood disadvantage screening for patients with, or at risk for developing chronic pain. Since the ADI allows for assessment of neighborhood disadvantage using readily available data, it may be a valuable tool in efforts to address chronic pain disparities, especially those based on geographically delineated SES inequality. An understanding of the level of neighborhood disadvantage of individuals and groups may be useful for the planning of patient care because it can help identify patients who would benefit from

interventions that address area-level SDOH. Regarding research implications, nurse scientists should investigate the effect of neighborhood on chronic pain outcomes using a longitudinal approach. Also, future studies should compare individual versus area level interventions in addressing SES disparities in chronic pain.

Conclusion

Individual and area factors correlate with cLBP outcomes such that lower income, lower education, and living in a disadvantaged neighborhood predicts cLBP severity and interference. To better understand the impact of SES on cLBP outcomes, both area-level and individual-level aspects of SES should be considered. Results generally fit with previously established findings that different measures of SES are related but not interchangeable. Among SES measures, income appears to be the strongest predictors of cLBP outcomes.

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EPIGENETIC AGE ACCELERATION MEDIATES THE RELATIONSHIP BETWEEN NEIGHBORHOOD DEPRIVATION AND PAIN SEVERITY IN ADULTS WITH KNEE OSTEOARTHRITIS PAIN

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Introduction

Pain is the primary symptom of knee osteoarthritis (KOA) and the main reason patients with KOA seek health care (Neogi, 2013). The global burden of KOA is high, estimated at 250 million people worldwide (Vos et al., 2012). It is a degenerative joint disease characterized by progressive wearing away of the articular cartilage (Hsu & Siwiec, 2022). As an age-related condition (Hsu & Siwiec, 2022), KOA is a leading cause of disability among older adults (Cross et al., 2014), with an estimated 25% of persons over age 55 years experiencing an episode of knee pain each year (Heidari, 2011). In addition to its connection to functional disability, multiple studies have detected an association between KOA and all-cause mortality (Hawker et al., 2014; Liu et al., 2015; Nüesch et al., 2011). To date, most studies have focused on the influence of chronological age and individual-level factors on KOA pain, leaving critical questions regarding the intersection of environmental and genetic factors.

Emerging evidence suggests a link between neighborhood socioeconomic status or disadvantage (i.e., neighborhood deprivation or living in a neighborhood with high levels of deprivation compared with national levels) and chronic pain (Fuentes et al., 2007; Green & Hart-Johnson, 2012; Jordan et al., 2008; Maly & Vallerand, 2018; Ulirsch et al., 2014). As it relates to this study, residents of high-deprivation neighborhoods are at greater risk of developing KOA (Reyes et al., 2015) and experiencing more severe KOA pain (Kopp et al., 2021). Such socioeconomic disparities in chronic pain are well documented (Grol-Prokopczyk, 2017; Janevic et al., 2017; Maly & Vallerand, 2018;

Zajacova et al., 2021), including worse outcomes for residents of high-deprivation neighborhoods (Fuentes et al., 2007; Green & Hart-Johnson, 2012; Jackson et al., 2021). High-deprivation neighborhoods have a high concentration of poverty and lack socioeconomic resource-based indicators such as employment and quality housing. These neighborhoods also lack many characteristics of the built environment that are needed to live a healthy life, like safety (Clark et al., 2013; Loh et al., 2018), walkability (Bereitschaft, 2017), as well as access to health care (Tsui et al., 2020), healthy foods (Hallum et al., 2020), and organized physical activities (Cohen et al., 2012). Residents of high-deprivation neighborhoods are more likely to experience multiple chronic conditions, even after controlling for other socioeconomic status measures (Chamberlain et al., 2020). However, the physiological underpinnings for neighborhood disparities in KOA are poorly understood.

Epigenetic modifications are environmentally sensitive changes in gene expression that have been proposed as a mechanism for the pathogenesis of chronic pain (Aroke et al., 2019; Buchheit et al., 2012; Denk & McMahon, 2012; Descalzi et al., 2015; Liang et al., 2015), including osteoarthritis pain (Reynard & Loughlin, 2012). Specifically, epigenetic modifications are stable and heritable alterations to the chromosome, primarily from environmental exposures that do not alter DNA sequences (Aristizabal et al., 2020). While there are several types of epigenetic changes (i.e., miRNA, long non-coding RNA, histone modifications), DNA methylation is the most well-studied epigenetic change (Lowe et al., 2015). DNA methylation refers to the covalent addition of a methyl group to the cytosine nucleotide of a DNA molecule. While some genes (or segments of genes) are normally methylated, exposure to internal and

external stimuli can change the level of DNA methylation, resulting in hyper- or hypomethylated segments (Meaney, 2010). These changes in DNA methylation may alter gene expression, thereby increasing or decreasing gene function, with subsequent changes in the production of proteins controlled by the associated genes (Brockie et al., 2013). Thus, various environmental exposures across the lifespan change the DNA methylation profile, alter health outcomes (Brockie et al., 2013), affect aging, and may help explain the development of age-related chronic conditions.

Several approaches have been developed that use DNA methylation patterns to estimate an individual's biological age, also called "epigenetic clocks" (Chen et al., 2016). Epigenetic clocks are strong predictors of chronological age (Simpson & Chandra, 2021), but some individuals' epigenetic/biological age does not correlate with chronological age. Epigenetic age acceleration (EpAA) represents epigenetic age advancing faster than actual chronological age (Fransquet et al., 2019; Hillary et al., 2020; McCartney et al., 2018; Perna et al., 2016). EpAA strongly correlates with age-related diseases, including chronic pain (Cruz-Almeida et al., 2019) and KOA pain outcomes (Strath et al., 2022), as well as all-cause mortality (Marioni et al., 2015; Zhang et al., 2017). Additionally, EpAA is associated with lower socioeconomic status (Fiorito et al., 2019; Fiorito et al., 2017; Hughes et al., 2018; Schmitz et al., 2022), including neighborhood deprivation (Lawrence et al., 2020; Lei et al., 2021; Lei et al., 2019). However, whether EpAA may explain the relationship between neighborhood deprivation and KOA pain severity remains unexplored. This study aims to determine if EpAA mediates the relationship between neighborhood deprivation and KOA pain severity.

Methods

Participants

This study is a secondary analysis of data collected as part of the larger Understanding Pain and Limitations in Osteoarthritic Disease (UPLOAD-2) study, which aims to understand mechanisms for racial/ethnic differences in knee pain. Participants were recruited as part of the parent study, and a full description of procedures for study enrollment has been published elsewhere (Bartley et al., 2019; Thompson et al., 2018). Briefly, individuals between the ages of 45-85 years with and without KOA were recruited from the University of Florida (Gainesville, Florida, USA) and the University of Alabama at Birmingham (Birmingham, Alabama, USA). Inclusion criteria included self-identification as non-Hispanic Black or non-Hispanic White and English-speaking. Exclusion criteria included: (a) major surgery to the most painful knee (e.g., total knee replacement), (b) diagnosis with a systemic rheumatic disease (e.g., fibromyalgia, systemic lupus erythematosus, rheumatoid arthritis), (c) cardiovascular disease or history of myocardial infarction, (d) uncontrolled hypertension (systolic > 150, diastolic > 95 mmHg), (e) major psychiatric illness, (f) pregnancy, (g) chronic opioid use, (h) neurological disease (e.g., multiple sclerosis, loss of sensory or motor function following stroke, Parkinson's), (i) neuropathy, or (j) substantial pain in a body site besides the knee. The institutional review boards of the University of Alabama at Birmingham (Birmingham, AL, USA) and the University of Florida (Gainesville, FL, USA) approved the study, and all participants provided written informed consent. The present study uses only data from participants with KOA, and only measures relevant to the aims of this ancillary study are presented below.

General Study Procedures

Demographic information, including age, ethnicity, sex, and addresses, were collected by self-report during an initial phone screening. Data collection occurred during two sessions. Informed consent was obtained prior to beginning the Health Assessment Session, followed by a health and pain history and physical exam. Participants attended a quantitative sensory testing (QST) session approximately 1 week later. Blood samples and clinical pain measures were collected during this second session. We accessed the data through a Limited Dataset Data Transfer Agreement approved by the University of Florida and the University of Alabama at Birmingham.

Measures

Graded Chronic Pain Scale

Knee osteoarthritis pain severity was assessed using the Graded Chronic Pain Scale (GCPS) intensity three-question subscale. The GCPS is a well-validated and reliable instrument to measure pain intensity and pain-related disability (Elliott et al., 2000). Using an 11-point Likert scale, participants were asked to rate their current, average, and worst pain over the last 6 months on a scale of 0–10, with 0 representing *no pain* and 10 representing *pain as bad as could be*. The GCPS pain intensity mean scores were multiplied by 10 to yield a score range of 0–100, with higher scores indicating greater pain.

Neighborhood Deprivation

We assessed neighborhood deprivation based on participants' nine-digit zip code using the Area Deprivation Index (ADI). The ADI is a well-validated instrument (Kind & Buckingham, 2018; Singh, 2003) that uses 17 census block indicators to create a score of the level of deprivation for a neighborhood. The census block indicators used to create the score capture the neighborhood-level socioeconomic domains of income, housing, employment, and education (Kind et al., 2014; Kind & Buckingham, 2018). We downloaded each participant's 2019 ADI v.3.1 state decile score from the developers' website (www.neighborhoodatlas.medicine.wisc.edu).

Blood Collection and Processing, DNA Extraction, and Methylation Analysis

Peripheral whole blood was collected from the forearm or hand into a 10ml ethylene-diamine-tetra-acetic acid (EDTA) anticoagulant tube. The EDTA tube was centrifuged at 3000 rpm for 10 minutes, and the buffy coat was harvested and stored in a cryovial at -80°C before DNA extraction. DNA was isolated by first thawing the buffy coat sample at 37°C to ensure homogenous dissolution. Approximately 150-200ul of the sample was then lysed in red blood cell lysis buffer and centrifuged at 6000 rpm at room temperature for 5 minutes. The supernatant was discarded, sodium EDTA solution was added to the precipitate, and then gently vortexed to resuspend. This suspension was incubated at 50-55°C with Proteinase K and SDS solution. After incubation, an equal volume of phenol was added, mixed, and centrifuged at 10,000 rpm for 10 minutes. The supernatant was harvested and transferred to a fresh tube. An equal volume of phenol-chloroform-isoamyl alcohol was added to the precipitate, mixed, and centrifuged at

10,000 rpm for 10 minutes. The supernatant was harvested and transferred to a fresh tube, and 1/10th the volume of 3M sodium acetate was added to the precipitate along with two volumes of absolute alcohol. The precipitated DNA was washed with 70% ethanol by centrifugation at 10,000 rpm for 5 minutes, after which the pellet was air dried and dissolved in Tris-EDTA buffer. The dissolved DNA was assessed for quality using qubit quantification and visualization on agarose gel. The Moffitt Cancer Center, Molecular Genomics Core (3011 Holly Dr., Tampa, FL 33612) performed the sodium bisulfite conversion and Illumina EPIC methylation array analysis.

Epigenetic Age Acceleration Calculation

Epigenetic age was calculated using the GrimAge method (Lu et al., 2019) via an online calculator (https://dnamage.genetics.ucla.edu/home). The EPIC array raw data (.idat files) underwent quality control and normalization before inputting into the calculator. The ChAMP (Chip Analysis Methylation Pipeline for Illumina HumanMethylation EPIC) protocol (Tian et al., 2017) was used to obtain normalized beta values. A subset of the normalized beta values was uploaded with a sample annotation file as directed by the online calculator's protocol document. EpAA was calculated as the difference between GrimAge and chronological age, which can be a positive or negative number, with positive values indicative of epigenetic age acceleration or an epigenetic age older than chronological age (Lawrence et al., 2020). The GrimAge clock was selected as the most suitable choice because, in our sample, it has previously been shown to relate most significantly with the experience of pain (Cruz-Almeida et al., 2022; Peterson et al., 2022; Strath et al., 2022)

Statistical Analyses

Data were analyzed using R version 4.1.0 statistical software. Before analyses, data were cleaned to include only the variables relevant to the present study. The relationships between pain severity, neighborhood deprivation, and measures of age were assessed using Spearman correlations, with the strength of the correlation coefficients classified as follows: negligible (< 0.10), weak (0.10–0.39), moderate (0.40–0.69), strong (0.70–0.89), and very strong (0.90–1.00) (Schober et al., 2018). Next, causal mediation analyses using the "mediation" R package were performed to determine whether epigenetic age acceleration mediated the relationship between neighborhood deprivation and KOA pain severity, with neighborhood deprivation as the predictor variable (X), epigenetic age acceleration as the mediator (M), and pain severity as the outcome variable (Y). The significance of the mediation model was tested using the bootstrap technique with 95% CI generated based on 1,000 simulations.

Results

Sample Characteristics

Of 245 participants recruited into the parent study, 128 participants with KOA who had complete pain, epigenetics, and neighborhood deprivation data were included in the present study sample. Participant characteristics are detailed in Table 1. The sample was mostly female (60.9%), had a mean chronological age of 58.3 years (± 7.9 years), and was approximately half non-Hispanic Black (49.2%) and half non-Hispanic White (50.1%). The mean pain severity score was 54.2 (± 23.1), and the mean EpAA was 2.9 years (± 5.9 years). The average neighborhood deprivation score was 6.0 (± 3.0).

Table 1

Characteristics of Participants (*N* = 128)

Characteristic	Mean (*SD*), Median (Range), % (*n*)
Chronological age (years)	58.3 (7.9)
GrimAge (years)	61.2 (7.7)
GrimAge EpAA (years)	2.9 (5.9)
Sex	
Male	39.1% (50)
Female	60.9% (78)
Ethnicity	
Non-Hispanic Black	49.2% (63)
Non-Hispanic White	50.8% (65)
Neighborhood Deprivation (1–10)	7.0 (1-10)
Pain Severity (0–100)	53.3 (10-100)

Pain Severity and Neighborhood Deprivation Associations With Measures of Chronological and Epigenetic Age

We used Spearman's bivariate correlations to establish the relationship between key variables. Pain severity positively correlated with EpAA and neighborhood deprivation and negatively correlated with chronological and epigenetic age. As shown in Table 2, the magnitude of the relationship with pain severity was strongest with EpAA ($\rho = 0.47$, $p < 0.001$), followed by chronological age ($\rho = -0.38$, $p < 0.001$), and neighborhood deprivation ($\rho = 0.25$, $p = 0.004$). Neighborhood deprivation positively

correlated with pain severity ($\rho = 0.25$, $p < 0.01$), epigenetic age acceleration ($\rho = 0.25$, $p < 0.01$), and epigenetic age ($\rho = 0.14$, $p > 0.05$). However, while the relationships between neighborhood deprivation and pain severity and between neighborhood deprivation and EpAA were significant ($p < 0.01$), the relationship between neighborhood deprivation and epigenetic age was not significant ($p > 0.05$). Even though we observed a negative correlation between pain severity and epigenetic age, it was not statistically significant, and the effect size was small ($\rho = -0.06$, $p > 0.05$).

Table 2

Spearman Correlations

	1.	2.	3.	4.	5.
1. Pain Severity	-				
2. Neighborhood Deprivation	0.25*	-			
3. Chronological Age	-0.38**	-0.04	-		
4. Epigenetic Age	-0.06	0.14	0.72**	-	
5. Epigenetic Age Acceleration	0.47**	0.25*	-0.44**	0.24*	-

*$p < 0.01$; **$p \leq 0.001$

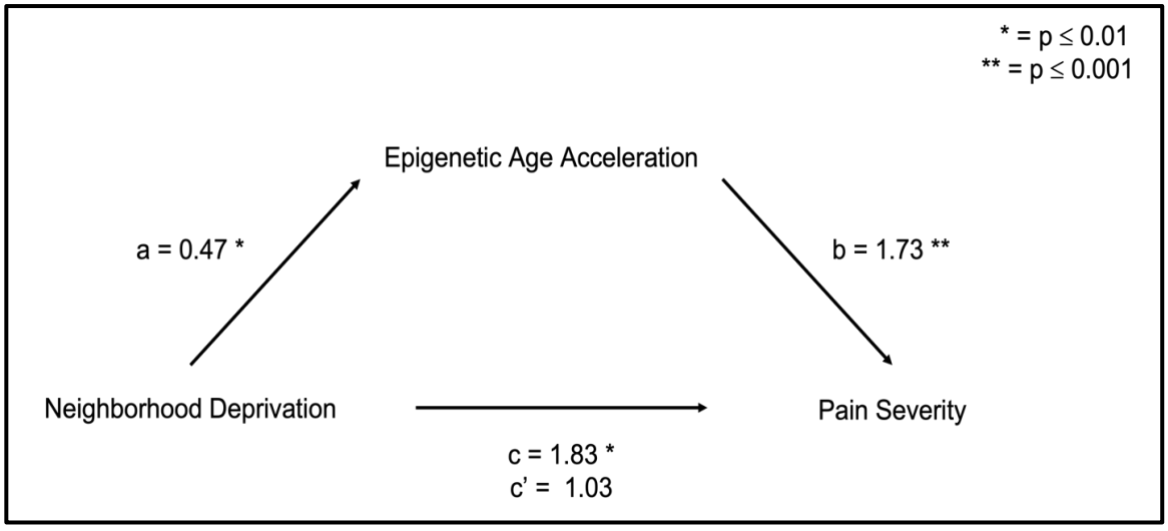
EpAA as Mediator of the Relationship Between Neighborhood Deprivation and Pain Severity

We used mediation models to explain the relationship between neighborhood deprivation and pain severity via EpAA. As depicted in Figure 1, EpAA mediates the relationship between neighborhood deprivation (predictor) and pain severity (outcome variable). Specifically, both paths **a** ($\beta = 0.47$, 95% CI = [0.13, 0.8], $p < 0.01$) and **b** ($\beta =$

1.73, 95% CI = [1.11, 2.35], $p < 0.001$) were significant, suggesting an indirect effect of neighborhood deprivation on pain severity through EpAA (path **a x b;** β = 0.81; CI [0.21, 1.51], $p = 0.006$). Mediation was confirmed as the direct effect of neighborhood deprivation on pain severity was no longer significant (path **c'**; β = 1.03, 95% CI = [-0.24, 2.32], $p = 0.12$) after adding EpAA to the model. There was a significant indirect effect of neighborhood deprivation on pain severity through EpAA, as the mediator accounted for a moderate portion of the total effect, PM = 0.44 (Figure 1).

Figure 1

Schematic of Mediation Model Including Neighborhood Deprivation (X), EpAA (M), and Pain Severity (Y)



Discussion

The purpose of this study was to determine if EpAA mediates the relationship between neighborhood deprivation and KOA pain severity. While there is a convincing link between lower socioeconomic status and chronic pain (Fuentes et al., 2007; Green &

Hart-Johnson, 2012; Jackson et al., 2021; Jordan et al., 2008; Ulirsch et al., 2014), fewer studies have specifically documented the connection between neighborhood deprivation and KOA pain. An exception was a population-based study in Catalonia, Spain, by Reyes et al. (2015). Using age-sex adjusted Incidence Rate Ratio (IRR), they found that living in the most deprived areas carried a greater risk of KOA (IRR = 1.51 [1.45 - 1.57]) compared to those living in the least deprived areas. To our knowledge, no studies have examined EpAA as a potential mediator of this relationship. Our findings add to a growing body of literature indicating that neighborhood deprivation is associated with EpAA and is an essential factor in chronic pain outcomes. Importantly, this study is the first to offer preliminary evidence that EpAA mediates the relationship between neighborhood deprivation and pain severity. Additionally, since KOA is an age-related condition, our findings offer the earliest evidence that EpAA may play a role in the relationship between neighborhood deprivation and age-related chronic conditions.

Our findings suggest that neighborhood deprivation is associated with worse KOA pain outcomes (i.e., severity). Living in high-deprivation neighborhoods has been associated with worse pain severity, interference, and physical functioning among adults with chronic low back pain (Jackson et al., 2021; Rassu et al., 2021; Rumble et al., 2021) and increased development of chronic pain following injury (Ulirsch et al., 2014). Our findings are consistent with these prior studies that link neighborhood deprivation and chronic pain (Jackson et al., 2021; Rassu et al., 2021; Rumble et al., 2021; Ulirsch et al., 2014) while extending the evidence of this connection to KOA pain.

Since KOA is an age-related condition (Cross et al., 2014; Heidari, 2011), our findings linking KOA pain severity and neighborhood deprivation are consistent with the

literature demonstrating a connection between neighborhood deprivation and age-related conditions. The burden of age-related conditions is greater in high-deprivation communities (Akwo et al., 2018; Claudel et al., 2018; Hu et al., 2021; Keita et al., 2014). For example, in a sample of participants in the southeastern United States, Akwo and colleagues (2018) found that a one-tertile increase in the level of neighborhood deprivation was associated with a 12% increase in risk for heart failure. Similarly, Claudel and colleagues (2018) found that among 1,989 participants, those living in the most deprived neighborhoods had 1.69 higher odds of developing hypertension. Likewise, Hu and colleagues (2021) found an increased diabetes prevalence ratio of 1.49 for residents of the most deprived neighborhoods compared to the least deprived. Our results support the assertation that neighborhood deprivation influences a range of age-related conditions.

This study is the first to demonstrate that EpAA mediates the relationship between neighborhood deprivation and KOA pain severity. Our findings agree with those of a prior study about EpAA mediation of a pain outcome. Strath and colleagues (2022) found that EpAA mediates the relationship between vitamin D and KOA pain severity and disability. Both studies drew their data from the same larger parent study, which limits our ability to make overreaching conclusions about EpAA as a mediator of chronic pain. Nevertheless, the studies' consistency does demonstrate promise for further inquiry into the mediating role EpAA may play for pain outcomes.

There is great interest in exploring epigenetic changes as a potential biological mechanism for the link between socioeconomic status and health outcomes (Cerutti et al., 2021; Evans et al., 2021; Martin et al., 2022). Epigenetic age has been convincingly

linked to age-related conditions (Fransquet et al., 2019; Hillary et al., 2020). Our findings further suggest that EpAA may act as a biological mechanism through which neighborhood deprivation influences age-related conditions such as KOA pain. However, studies investigating epigenetic age as a mediator in a relationship between a predictor and an age-related disease outcome are limited. Exceptions include a study by Joyce and colleagues (2021), who found that EpAA mediates the relationship between cardiovascular risk factors and coronary artery calcification. An additional study by Klopack and colleagues (2022) found that epigenetic age mediates the association between exposure to smoking and the outcomes of cancer, high blood pressure, heart disease, and mortality. However, despite the interest in epigenetic explanations for how socioeconomic status affects health, none of these studies examined epigenetic age as a potential mediator for neighborhood deprivation or socioeconomic status as a predictor. The present study fills this gap and agrees with the findings of prior studies that epigenetic aging may mediate age-related disease outcomes.

Strengths and Limitations

The major strength of this study is that, to our knowledge, it is the first that addresses the keen interest and lack of literature on EpAA as a mediator for socioeconomic status as a predictor of KOA pain. Another strength is that despite the relatively small sample size, it included representation from 2 distinct sites in the US, including both women and men and non-Hispanic Black and non-Hispanic White participants, increasing the generalizability of our findings.

Despite the above strengths, we acknowledge some limitations to our study. First, in our analysis, epigenetic age was calculated based on only one epigenetic clock, and different clocks may vary in their results. There is some evidence that different clocks may measure different disease susceptibilities (Macdonald-Dunlop et al., 2022), so the choice of epigenetic clock used for analysis is an important consideration. However, in the present study, we used the GrimAge epigenetic clock (Lu et al., 2019). GrimAge performs well as an epigenetic clock, strongly correlating with chronological age, morbidity, and mortality (Hillary et al., 2020; Li et al., 2020; Lo & Lin, 2022; McCrory et al., 2021; Morales Bernstein et al., 2022). More importantly, the GrimAge clock has been associated with KOA pain outcomes in this participant cohort (Cruz-Almeida et al., 2022; Strath et al., 2022) and has also been linked to neighborhood deprivation (Lawrence et al., 2020; Lei et al., 2021). So, even though only one epigenetic clock was used in our analysis, GrimAge was the ideal choice.

Second, our analysis did not include controlling for other measures of socioeconomic status. Various socioeconomic variables may influence pain outcomes (Bonathan et al., 2013). However, in this study, neighborhood deprivation was measured using the ADI, a composite of socioeconomic status for a given census block. By design, the ADI score is a congregate of the socioeconomic measures of the individuals living in the neighborhood. Consequently, our neighborhood-level socioeconomic status measurement is highly correlated to individual-level socioeconomic status measures and would thus have potentially created collider bias. Collider variables distort the interpretation of an association between predictor and outcome variables because they influence both the predictor and outcome variables (Cole et al., 2010). Thus, it was

inappropriate to control for other individual measures of socioeconomic status in our analyses.

Conclusion

Neighborhood deprivation is an important factor in age-related conditions such as KOA pain. Our findings suggest that EpAA may be a biological process by which neighborhood deprivation is related to KOA pain severity. Since epigenetic changes are dynamic and reversible, future studies can investigate ways to slow the aging process and treat KOA pain epigenetically. Continuing to explore epigenetic aging as a mechanism for pain outcomes may lead to opportunities for intervention.

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CONCLUSIONS

This dissertation aimed to examine the relationship between neighborhood deprivation, chronic musculoskeletal pain outcomes, and EpAA in adults. We accomplished this goal in three manuscripts. The first manuscript reviewed the literature for evidence of the relationship between neighborhood characteristics and epigenetic age acceleration (EpAA). The second compared neighborhood deprivation with other measures of socioeconomic status (SES) as predictors of chronic low back pain (cLBP) outcomes. The third reported the relationship between neighborhood deprivation, epigenetic age acceleration, and KOA pain. Specifically, we use a mediation analysis to explain that EpAA (mediator) explained the underlying relationship between neighborhood deprivation and pain severity among adults with KOA. This chapter presents a brief overview of the findings from each manuscript, integrating the knowledge gained and contribution to nursing science. Additionally, this chapter discusses the strengths and limitations of the dissertation as well as its implications for future research and practice.

Overview of Study Findings

Manuscript 1: Neighborhood Environment and Epigenetic Age: A Scoping Review

We synthesized existing evidence of the relationship between neighborhood environment and epigenetic age using the scoping review methodology guidelines

suggested by Arksey and O'Malley (2005). All studies were published since 2019, a testament to the fact that the study of this relationship is an emerging area of focus. Most studies examined deprivation as the neighborhood characteristic of interest, with only one study focusing exclusively on a physical neighborhood characteristic—greenness (Xu et al., 2021). While all studies were observational in design, the articles included diverse participants, including men and women, adults and children, and multiple ethnicities. Overall, studies concluded there was a relationship between neighborhood characteristics and epigenetic age, whether the characteristic of interest was socioeconomic or physical. However, the paucity of investigations on physical neighborhood characteristics is noticeable, especially since aspects of the physical environment (such as particulate matter, noise, and heat) have been linked to age-related conditions such as cardiovascular disease. This review described the scope of the evidence on the relationship between neighborhood deprivation and epigenetic age, supporting investigations that extend work in the area, such as the study reported in manuscript three. The findings of manuscript one also demonstrated that GrimAge is suitable for use in studies of neighborhood deprivation and for racially diverse samples, which helped inform the choice of the epigenetic clock for the main study reported in manuscript three.

Manuscript 2: The Area Deprivation Index Corresponds Effectively With Other Measures of Objective Socioeconomic Status in Adults With Chronic Low Back Pain

Manuscript two compared the Area Deprivation Index (ADI), a measure of neighborhood SES, with other individual measures of SES in its ability to predict cLBP

outcomes. For this secondary data analysis, we included 104 adult participants from the ongoing Examining Racial and SocioEconomic Disparities in Chronic Low Back Pain (ERASED) (R01MD010441) study. Most participants were women (58.7%) and non-Hispanic Black (56.7%), with an average age of 45. At $35,000-39,900, the median household income for the sample was below Alabama ($48,000) and national ($60,000) averages. Most participants (74%) had some college education, graduated from college, or attended graduate school. Area Deprivation Index scores were available for 97% of participants, representing 85 census block groups located in five counties in central Alabama. Self-rated subjective social status was rated as 5.1 (SD = ± 2.0) out of 10. The ADI was compared with income, education, and subjective social status. We detected no significant relationship between subjective social status and pain severity/interference and omitted subjective measures from further analysis. Pain severity positively correlated with ADI (r = 0.396) and negatively with income (r = - 0.507) and education (r = - 0.271). Similarly, pain interference positively correlated with ADI (r = 0.33), and negatively with income (r = - 0.428) and education (r = - 0.102). Simple linear models of ADI, income, and education were regressed on pain incomes. Goodness-of-fit-testing using Akaike information criterion (AIC) and Bayesian information criterion (BIC) was performed, comparing each measure's ability to predict pain severity/interference. For pain severity, the models' goodness-of-fit AIC and BIC suggested that income outperforms other measures of SES (AIC = 428.29/BIC = 436.22), followed by ADI (AIC = 437.24/BIC = 445.17), with education performing least well (AIC = 446.35/BIC = 454.29). Similar results were seen for pain interference, with income performing best (AIC = 456.08/BIC = 464.01), followed closely by ADI (AIC = 463.96/BIC = 471.90).

Finally, the multiple regression model of ADI, income, and education on pain outcomes revealed that, while income makes the largest contribution to pain severity (partial R^2 = 0.98) and pain interference (partial R^2 = 0.100), ADI makes a small significant independent contribution to both pain severity (partial R^2 = 0.021) and pain interference (partial R^2 = 0.029). These findings suggest that neighborhood SES performs as well as other individual measures of SES in predicting cLBP outcomes and outperforms some frequently used measures (i.e., education, subjective social status). Furthermore, the results demonstrate that neighborhood-level SES contributes to pain outcomes independently of individual-level SES factors, which supports the need for a biological mechanism study, as reported in manuscript three.

Manuscript 3: Epigenetic Age Acceleration Mediates the Relationship Between Neighborhood Deprivation and Pain Severity in Adults With Knee Osteoarthritis Pain

To examine the potential underlying mechanism driving musculoskeletal pain outcomes, we examined whether EpAA mediates the relationship between neighborhood deprivation and pain severity in adults with KOA. We conducted a secondary, cross-sectional analysis of data collected as part of the Understanding Pain and Limitations in Osteoarthritic Disease (UPLOAD-2). The sample of 128 participants was mostly female (60.9%), approximately half non-Hispanic Black (49.2%), and had a mean age of 58 years. The mean pain severity score was 54.2 (± 2.31) out of a possible score of 0–100, and the mean EpAA was 2.9 years (± 5.9 years). The neighborhood deprivation score average was 6.0 (± 3.0) out of a possible score of 0–10. Spearman bivariate correlations

revealed that pain severity positively correlated with EpAA ($\rho = 0.47$, $p \leq 0.001$) and neighborhood deprivation ($\rho = 0.25$, $p = 0.004$) and negatively correlated with chronological age ($\rho = -0.38$, $p \leq 0.001$). We found a positive significant relationship between neighborhood deprivation and EpAA ($\rho = 0.47$, $p \leq 0.001$). However, the correlations between pain severity or neighborhood deprivation and epigenetic age were not significant.

Mediation models were used to explain the relationship between neighborhood deprivation and pain severity via EpAA. The results indicate that EpAA mediates the relationship between neighborhood deprivation (predictor) and pain severity (dependent variable). Specifically, both paths **a** ($\beta = 0.47$, 95% CI = [0.13, 0.8], $p < 0.01$) and **b** ($\beta = 1.73$, 95% CI = [1.11, 2.35], $p < 0.001$) were significant, suggesting an indirect effect of neighborhood deprivation on pain severity through EpAA (path **a x b**; $\beta = 0.81$; CI [0.21, 1.51], $p = 0.006$). Mediation was complete as the direct effect of neighborhood deprivation on pain severity was no longer significant (path **c'**; $\beta = 1.03$, 95% CI = [-0.24, 2.32], $p = 0.12$) after adding EpAA to the model. There was a significant indirect effect of neighborhood deprivation on pain severity through EpAA, as the mediator accounted for a moderate portion of the total effect, PM = 0.44. To our knowledge, this study is the first to examine EpAA as a mediator of neighborhood deprivation and a KOA pain outcome. These findings suggest that EpAA may be a mechanism through which neighborhood deprivation leads to worse chronic musculoskeletal pain outcomes like increased KOA pain severity. Furthermore, since chronic musculoskeletal pain is an age-related condition, this study suggests that EpAA may play a role in the well-documented relationship between the neighborhood of residence and age-related diseases.

Integrated Interpretation of Findings

When exploring social determinants of health and health disparities, many studies have documented that an individual's zip code may be a stronger predictor of health outcomes than their genetic code (Graham, 2016). Living in a high-deprivation neighborhood has been linked to poor age-related chronic disease outcomes. Even though a growing number of voices recognize the role that residential neighborhoods may play in pain disparities, there is a lack of consistent data to evaluate and understand these relationships. Ultimately, this limitation may impede the development of effective strategies to eliminate pain disparities. The findings from our literature review (manuscript one) suggest that neighborhood characteristics are significantly associated with epigenetic age. Specifically, negative neighborhood characteristics like neighborhood deprivation correlate with EpAA, while positive characteristics like a larger degree of neighborhood greenness are associated with epigenetic age deceleration. Other investigators have suggested that neighborhood deprivation may be linked to allostatic load, with higher neighborhood deprivation correlating with higher allostatic load (Ribeiro et al., 2018). Allostatic load refers to overextension of the body's ability to cope with environmental stressors, leading to the deterioration of health (McEwen, 1998)—a concept that shares ties with the wear and tear hypothesis that guided this dissertation.

Epigenetic modifications are mechanisms by which chronic stress affects health outcomes without changing the DNA sequence. A review by Cerutti et al. (2021) found that SES is associated with both genome-wide DNA methylation and differential methylation of candidate genes (Cerutti et al., 2021). Another review concluded that

neighborhood deprivation is linked to differential DNA methylation, particularly of genes related to stress and inflammation (Giurgescu et al., 2019). Manuscript one adds to this body of literature while making a unique contribution to reviews on the relationship between neighborhood and epigenetics. Our review expanded the scope of potential epigenetic modifiers beyond SES to all neighborhood characteristics, finding that the neighborhood environment's physical characteristics are likely influential in affecting epigenetic aging.

In alignment with these reviews, manuscript one supports the role of SES in epigenetic modifications. While the findings from manuscript one showed that neighborhood SES is convincingly associated with epigenetic age, they did not reveal how well neighborhood SES performs as a predictor of health outcomes compared to individual-level measures of SES—specifically, how neighborhood SES compares to individual SES in predicting musculoskeletal pain outcomes. This gap was addressed in manuscript two. Furthermore, considering the strong correlation between EpAA and age-related conditions (Hillary et al., 2020), in addition to highlighting the convincing correlation between neighborhood SES and epigenetic age, manuscript one also revealed that there is a critical need for studies that examine the influence of EpAA on the relationship between neighborhood SES and age-related conditions. This gap was addressed in manuscript three.

The inclusion of all neighborhood characteristics in the examination of the relationship with epigenetic age revealed that there is a lack of studies on the influence of physical neighborhood characteristics. Several features of the physical neighborhood environment have been associated with age-related disease outcomes. For example, air

pollution has been linked to increased cardiovascular-related hospitalizations and cardiovascular disease-related mortality (Brook et al., 2004). Exposure to air particulate matter, pollutants, and residential noise has been found to correlate with an increased risk for type 2 diabetes (Beulens et al., 2022). Noise has also been connected to hypertension and stroke (Münzel et al., 2014). Additionally, aspects of the neighborhood built environment, such as walkability and access to healthy food, have been associated with cardiovascular disease outcomes (Malambo et al., 2016). Despite their importance to age-related disease outcomes, to the best of our knowledge, many physical neighborhood characteristics such as these have yet to be examined in relation to epigenetic age. Considering the strong correlation between EpAA and age-related diseases, these and other features of the physical neighborhood environment warrant study in relation to epigenetic age.

Our study comparing individual versus neighborhood measures of SES as predictors of pain outcomes reveals two significant findings. First, neighborhood deprivation is an important predictor of musculoskeletal pain outcomes. These findings are consistent with previous studies suggesting that living in high-deprivation neighborhoods is associated with increased musculoskeletal pain and more significant interference with daily activities from pain following a motor vehicle accident (Ulirsch et al., 2014). Likewise, increased noninflammatory musculoskeletal pain interference has been noted among residents of high-deprivation neighborhoods in Norway (Brekke et al., 2002). Fuentes et al. (2007) observed that residence in low-deprivation neighborhoods is associated with lower chronic pain disability in adults over the age of 50 years. Thus, the study reported in manuscript two joins the consensus with this prior research to support

the examination of neighborhood deprivation as a predictor of pain outcomes. Specifically, this is the first study to show a relationship between neighborhood deprivation and cLBP; for adults with cLBP, ADI may be a good predictor of pain outcomes.

The second significant finding from manuscript two is that area-level measures of SES may be as effective and outperform some individual measures of SES in predicting pain outcomes. In fact, the strength of the relationships between area- and individual-level measures of SES was slightly higher in this study compared to prior literature. Our findings suggest a moderate relationship, while Diez-Roux et al. (2001) detected only weak correlations between area- and individual-level measures of income in an examination of three U.S.-based cohorts. Likewise, Buajitti et al. (2020) reported a low correlation between area- and individual-level SES in the population-based Canadian Community Health Survey. Differences in the strength of the relationship between area- and individual-level measures may be related to the fact that while measures of SES are related, SES as a phenomenon is multidimensional (Galobardes et al., 2007; Krieger et al., 1997) and so may be best captured using a multidimensional measure. Mindful of this notion, to measure neighborhood deprivation we used ADI, which relies on 17 different indicators capturing aspects of income, education, and housing, to assess the level of deprivation. Conversely, Buajitti and colleagues (2020) used only area-level income to compare individual- and area-level measures of SES. The multidimensional nature of the ADI may help explain why area-level SES performed better in our study compared to previous literature.

While the above evidence suggested a relationship between neighborhood deprivation and musculoskeletal pain, the underlying biological mechanism driving this relationship remained unclear. The key findings from manuscript three suggest that EpAA mediates the relationship between neighborhood deprivation and KOA pain severity. These findings add to the literature on the relationship between chronic musculoskeletal pain and neighborhood deprivation by providing, for the first time, a potential underlying explanation for worse musculoskeletal pain outcomes in poor neighborhoods. Since KOA is an age-related condition, our findings suggest that living in a high-deprivation neighborhood may induce accelerated epigenetic aging, which explains worse KOA pain severity. Thus, EpAA may play a crucial role in the well-documented link between neighborhood deprivation and other age-related conditions. Studies investigating epigenetic age as a mediator or a predictor of age-related diseases, especially chronic pain outcomes, are limited. Joyce and colleagues (2021) found that EpAA mediated the relationship between cardiovascular risk factors and coronary artery calcification. Strath and colleagues (2022) found that EpAA mediates the relationship between vitamin D and KOA pain outcomes, while Klopack and colleagues (2022) found that epigenetic age mediated the association between exposure to smoking and the outcomes of cancer, high blood pressure, heart disease, and mortality. There is a growing interest in the relationship between epigenetic changes, SES, and health outcomes. Our findings are the first to indicate that accelerated epigenetic aging may mediate the relationship between neighborhood deprivation and age-related disease outcomes, providing a potential target for future interventions.

Strengths and Limitations

This dissertation had some significant strengths. First, manuscripts two and three offer new evidence on the relationship between neighborhood deprivation and chronic musculoskeletal pain in not only one but two different body sites—the lower back and knee. Second, both data-driven studies used diverse samples, including both men and women, with roughly half of the participants self-identifying as non-Hispanic Black. This diversity allows the findings to be more generalizable. Another strength of this dissertation was using two different instruments to measure pain severity (i.e., Brief Pain Inventory and Graded Chronic Pain Scale), reducing the likelihood that the relationship between neighborhood deprivation and pain severity is due merely to chance. Related to methodology, the findings from manuscript one revealed that there could be variation in analysis results depending on race and the type of neighborhood characteristic being assessed. Using GrimAge for estimating EpAA was a strength because GrimAge has been used successfully in neighborhood deprivation studies and racially diverse samples. Since our analysis examined neighborhood deprivation in a racially diverse sample, it was the ideal choice for the mediation analysis reported in manuscript three. Finally, using two different musculoskeletal pain conditions was a strength as it supports the role of epigenetic modifications across chronic pain conditions.

Despite the above strengths, this dissertation is not without limitations. The findings reported in manuscripts two and three relied on secondary data analysis. A disadvantage inherent to the nature of secondary data analysis is that the data were not collected specifically to address the research questions of the current study (Cheng & Phillips, 2014). Although not the original focus, this dissertation's exploration of

neighborhood deprivation aligned with the goals of both parent studies, whose data were used in manuscripts two and three. Examining socioeconomic factors involved in chronic pain was a goal for both parent studies. So, this dissertation's analysis of the relationship between neighborhood-level SES with pain outcomes remained in keeping with the broad goals and intentions of the parent studies. Another limitation is that residential information used for this dissertation study may have been applicable only at the time of data collection. The length of participants' residence in their neighborhood was unknown, and the length of time exposed to neighborhood deprivation could impact pain and EpAA. Also, though the pain data-driven studies (manuscripts two and three) used separate cohorts, both drew participants only from the deep South of the United States, thereby limiting our findings of area-level associations with pain and EpAA to this region. Finally, it is essential to note that while this dissertation's findings support the central hypothesis that neighborhood deprivation may lead to EpAA resulting in chronic pain, the correlational design limits interpretations about neighborhood deprivation playing a causal role in EpAA and worse chronic pain outcomes.

Implications for Future Research and Practice

This body of work provides several implications for future research and practice. There is a paucity of studies examining neighborhood characteristics *beyond* neighborhood SES. With our perspective and training in serving the community as the client, nurse scientists are well equipped to lead investigations that center on uncovering the many as yet unexplored neighborhood-level contributors to EpAA and the development of age-related conditions. Future studies should examine these non-

socioeconomic neighborhood characteristics, such as particulate matter, noise, and heat. Additionally, since the length of time exposed to neighborhood environmental factors is likely salient to their impact on epigenetic changes, there is a need for longitudinal studies exploring neighborhood effects on EpAA over time.

Our findings suggesting that neighborhood deprivation is associated with worse chronic musculoskeletal pain outcomes and with EpAA have research and practice implications. These results have relevance to nursing practice, particularly for public health nurses who must consider the role of the environment in health outcomes. Public health nurses should advocate for policies to eliminate neighborhood disparities, focusing on improving health at the population/community level. These findings support the need for an integrative approach in dealing with social determinants of health, as environmental factors such as those in the neighborhood environment may be driving epigenetic changes associated with individual disease vulnerabilities.

Finally, since epigenetic modifications are reversible, our findings provide potential targets for interventions. Future studies may include interventions to reverse or slow epigenetic aging. Solid recommendations for interventions cannot be made based solely on conclusions from this observational study. Thus, additional studies are needed to replicate and validate the findings from manuscript three that EpAA mediates the relationship between neighborhood deprivation and pain severity, justifying future intervention studies.

Conclusions

Residents of high-deprivation neighborhoods experience worse pain outcomes and may live 20 fewer years than residents of low-deprivation neighborhoods in the same city. While this phenomenon has been noted for generations, the physiological pathways for this relationship in adults with chronic musculoskeletal pain are understudied and poorly understood. The findings from the three manuscripts add to the body of literature on the relationship between neighborhood deprivation and chronic pain, as well as the connection between neighborhood deprivation and EpAA. Our literature review in manuscript one identified mounting evidence for an association between neighborhood deprivation and EpAA and identified several gaps in the literature, which we addressed using empirical data. In manuscript two, we found that neighborhood deprivation was a strong predictor (even better than some conventional individual SES measures) of cLBP. The findings from manuscript three support a growing consensus that neighborhood deprivation may lead to EpAA, which also correlates with more severe KOA pain. Together these results suggest that epigenetic modifications may explain the relationship between residential neighborhoods and chronic pain outcomes. While additional studies are needed to verify this link, this work provides a preliminary understanding of how living in a poor neighborhood can result in worse pain.

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APPENDIX A

UNIVERSITY OF ALABAMA AT BIRMINGHAM INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

UAB INTEGRATED RESEARCH ADMINISTRATION PORTAL

IRB Personnel eForm

GENERAL INFORMATION

PROJECT OVERVIEW

Project Title Racial and Socioeconomic Differences in Chronic Low Back Pain

IRB Project Number IRB-170119003

Investigator Assurance
- All key personnel listed on the protocol have completed initial IRB training and have or will complete continuing IRB training as required, and
- All personnel are qualified and licensed/credentialed for the procedures they will be performing, if applicable.

PERSONNEL

Click here to add new key personnel. See the Key Personnel Flowchart.

To remove personnel, enter an end date into the personnel record below.

See the Other Personnel section of this form for how to add UAB, Children's of Alabama, Lakeshore, or BVAMC staff members not in the picklist. All other non-affiliated personnel should be added via Project Revision/Amendment Form.

FDA: For studies involving investigational drugs, list all investigators who will be listed on FDA Form 1572 and include a copy of the 1572. Send the IRB a copy of Form 1572 any time you update the form with the FDA.

Name
Jackson, Pamela

Email	jacksop2@uab.edu
Department	Nursing Acad Affairs

Principal Investigator	Start Date	End Date	* Role
☐	15-May-2019		Other Personnel

Certifications

Certification	Begin	End
IRB Initial Training - CITI	04-Apr-2019	04-Apr-2022
IRB ICH-GCP	06-May-2019	06-May-2022
Financial Conflict of Interest	30-Jan-2020	30-Jan-2024
Financial Conflict of Interest in Research - 4th Yr Refresher	12-Nov-2020	12-Nov-2024

Degree

Training certificates

Indicate the following activities in which this individual will be involved. If this individual is not involved in any of these activities, he/she should not be listed as key personnel on the IRB submission:

- ☐ Involved in the design of the human subjects research
- ☑ Obtaining informed consent*
- ☑ Interacting/intervening with participants for research purposes
- ☑ Obtaining private identifiable data or identifiable specimens
- ☐ Administering investigational (non-FDA-approved) product (e.g., drug, device, or biologic)
- ☐ Named on the FDA 1572 or device agreement*
- ☐ Required to complete sponsor's conflict of interest form*

Yes Is the individual named above "responsible" for the design, conduct, or reporting of the research?

No Will the individual named above be involved in explaining the study, risk-benefit, and/or alternatives to potential participants?

No Does this individual have a financial interest in this project (see below for definition)?

Please note: Individuals in a role of PI, Co-PI, and/or Faculty Advisor, as well as anyone who is involved in an activity marked with an asterisk, or answers yes to one of the additional questions related to responsible personnel above must file a disclosure of financial interests and complete training requirements of the UAB CIRB .

APPENDIX B

DATA TRANSFER AND USE AGREEMENT

Agreement ID: AGR00025510

FDP Data Transfer and Use Agreement ("Agreement")

Provider: University of Florida Board of Trustees	Recipient: The Board of Trustees of the University of Alabama for the University of Alabama at Birmingham
Provider Scientist Name: Yenisel Cruz-Almeida Email: cryeni@ufl.edu	Recipient Scientist Name: Edwin Aroke Email: earoke@uab.edu
Agreement Term Start Date: 6/13/2022 End Date: Three (3) Years after the Start Date	Project Title: Neighborhood Deprivation and Epigenetic Age Acceleration in Chronic Pain Attachment 2 Type: Limited Data Set

Terms and Conditions

1) Provider shall provide the data set described in Attachment 1 (the "Data") to Recipient for the research purpose set forth in Attachment 1 (the "Project"). Provider shall retain ownership of any rights it may have in the Data, and Recipient does not obtain any rights in the Data other than as set forth herein.
2) If applicable, reimbursement of any costs associated with the preparation, compilation, and transfer of the Data to the Recipient will be addressed in Attachment 1.
3) Recipient shall not use the Data except as authorized under this Agreement. The Data will be used solely to conduct the Project and solely by Recipient Scientist and Recipient's faculty, employees, fellows, students, and agents ("Recipient Personnel") and Collaborator Personnel (as defined in Attachment 3) that have a need to use, or provide a service in respect of, the Data in connection with the Project and whose obligations of use are consistent with the terms of this Agreement (collectively, "Authorized Persons").
4) Except as authorized under this Agreement or otherwise required by law, Recipient agrees to retain control over the Data and shall not disclose, release, sell, rent, lease, loan, or otherwise grant access to the Data to any third party, except Authorized Persons, without the prior written consent of Provider. Recipient agrees to establish appropriate administrative, technical, and physical safeguards to prevent unauthorized use of or access to the Data and comply with any other special requirements relating to safeguarding of the Data as may be set forth in Attachment 2.
5) Recipient agrees to use the Data in compliance with all applicable laws, rules, and regulations, as well as all professional standards applicable to such research.
6) Recipient is encouraged to make publicly available the results of the Project. Before Recipient submits a paper or abstract for publication or otherwise intends to publicly disclose information about the results of the Project, the Provider will have thirty (30) days from receipt to review proposed manuscripts and ten (10) days from receipt to review proposed abstracts to ensure that the Data is appropriately protected. Provider may request in writing that the proposed publication or other disclosure be delayed for up to thirty (30) additional days as necessary to protect proprietary information.

Agreement ID: AGR00025510

7) Recipient agrees to recognize the contribution of the Provider as the source of the Data in all written, visual, or oral public disclosures concerning Recipient's research using the Data, as appropriate in accordance with scholarly standards and any specific format that has been indicated in Attachment 1.

8) Unless terminated earlier in accordance with this section or extended via a modification in accordance with Section 13, this Agreement shall expire as of the End Date set forth above. Either party may terminate this Agreement with thirty (30) days written notice to the other party's Authorized Official as set forth below. Upon expiration or early termination of this Agreement, Recipient shall follow the disposition instructions provided in Attachment 1, provided, however, that Recipient may retain one (1) copy of the Data to the extent necessary to comply with the records retention requirements under any law, and for the purposes of research integrity and verification.

9) Except as provided below or prohibited by law, any Data delivered pursuant to this Agreement is understood to be provided "AS IS." PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE DATA WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. Notwithstanding, Provider, to the best of its knowledge and belief, has the right and authority to provide the Data to Recipient for use in the Project.

10) Except to the extent prohibited by law, the Recipient assumes all liability for damages which may arise from its use, storage, disclosure, or disposal of the Data. The Provider will not be liable to the Recipient for any loss, claim, or demand made by the Recipient, or made against the Recipient by any other party, due to or arising from the use of the Data by the Recipient, except to the extent permitted by law when caused by the gross negligence or willful misconduct of the Provider. No indemnification for any loss, claim, damage, or liability is intended or provided by either party under this Agreement.

11) Neither party shall use the other party's name, trademarks, or other logos in any publicity, advertising, or news release without the prior written approval of an authorized representative of that party. The parties agree that each party may disclose factual information regarding the existence and purpose of the relationship that is the subject of this Agreement for other purposes without written permission from the other party provided that any such statement shall accurately and appropriately describe the relationship of the parties and shall not in any manner imply endorsement by the other party whose name is being used.

12) Unless otherwise specified, this Agreement and the below listed Attachments embody the entire understanding between Provider and Recipient regarding the transfer of the Data to Recipient for the Project:

   I. Attachment 1: Project Specific Information
   II. Attachment 2: Data-specific Terms and Conditions
   III. Attachment 3: Identification of Permitted Collaborators (if any)

13) No modification or waiver of this Agreement shall be valid unless in writing and executed by duly-authorized representatives of both parties.

Agreement ID: AGR00025510

14) The undersigned Authorized Officials of Provider and Recipient expressly represent and affirm that the contents of any statements made herein are truthful and accurate and that they are duly authorized to sign this Agreement on behalf of their institution.

By an Authorized Official of Provider:

Sherrie R Bowen 7/31/2022 | 2:48 PM EDT

Date

Name: Sherrie R. Bowen, JD, CRCP

Title: OCR Contracting Team Lead

Contact Information for Formal Notices:

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Phone: 352-273-5946

Signature: Melinda T. Cotten

Email: mcotten@uab.edu

07/19/2022

Date

Name: Melinda T. Cotten

Title: Associate Vice President Research Business Op.

Contact Information for Formal Notices:

Name: Office of Sponsored Programs

Address: 1720 2nd Ave South
AB 1170
Birmingham, AL 35294-0111

Email: osp@uab.edu

Phone: 205-934-5266

Agreement ID: AGR00025510

Attachment 1
Data Transfer and Use Agreement
Project Specific Information

1. Description of Data:
   More detail to be provided by UF Study Team

   Epigenetic data, clinical measurements, socioeconomic variables, and demographics.

2. Description of Project:
   This project will investigate the relationship between neighborhood deprivation and epigenetic age acceleration in chronic pain.

3. Provider Support and Data Transmission:

   Provider shall transmit the Data to Recipient: (select one) ☑ electronically or ☐ by mail to:

Name:	Edwin Aroke
Address:	1720 2nd Avenue S Birmingham, AL 35294-1210
Email:	earoke@uab.edu
Phone:	205-975-5700

DocuSign Envelope ID: 8E483B5C-4BED-4171-BB9B-911E408B187B

Agreement ID: AGR00025510

Upon execution of this Agreement, Provider shall send any specific instructions necessary to complete the transfer of the Data to the contact person listed above, if not already included below in this section of Attachment 1.

* Format of the Data
* Provision of the Data dictionary
* Availability of the Provider to assist the Recipient in understanding the Data structure (e.g. variables, code lists, etc.)
* If/how the Data will be revised and resent if errors are found by the Recipient
* Specific instructions necessary to complete the transmission of the Data, if available/appropriate, and any support supplied by the Provider for the transmission
* Specific instructions regarding public disclosures and other scholarly standards.

4. Reimbursement of Costs:

☑ None

☐ As governed by a separate written agreement between the parties
Reimbursement Agreement Reference # (if required):
_____

☐ As set forth herein:

5. Disposition Requirements upon the termination or expiration of the Agreement:
The Recipient will return or destroy all copies of the Data in accordance with the Provider's instructions at time of Agreement termination or expiration.

Agreement ID: AGR00025510

Attachment 2
Data Transfer and Use Agreement
Data-specific Terms and Conditions:
Limited Data Set

Additional Terms and Conditions:

1. Nothing herein shall authorize the Recipient to use or further disclose the Data in a manner that would violate the requirements of Provider under 45 CFR 164.514.

2. Recipient shall not use or further disclose the Data other than as permitted by this Agreement or as otherwise required by law.

3. Recipient shall report to the Provider any use or disclosure of the Data not provided for by this Agreement within 5 business days of when it becomes aware of such use or disclosure.

4. Provider is a HIPAA Covered Entity, and the Data will be a Limited Data Set as defined by the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"). In accordance with Section 164.514(e)(2) of the HIPAA Privacy Rule, the Data shall exclude the following direct identifiers of the individual or of relatives, employers, or household members of the individual:
   (i) Names;
   (ii) Postal address information, other than town or city, State, and zip code;
   (iii) Telephone numbers;
   (iv) Fax numbers;
   (v) Electronic mail addresses;
   (vi) Social security numbers;
   (vii) Medical record numbers;
   (viii) Health plan beneficiary numbers;
   (ix) Account numbers;
   (x) Certificate/license numbers;
   (xi) Vehicle identifiers and serial numbers, including license plate numbers;
   (xii) Device identifiers and serial numbers;
   (xiii) Web Universal Resource Locators (URLs);
   (xiv) Internet Protocol (IP) address numbers;
   (xv) Biometric identifiers, including finger and voice prints; and
   (xvi) Full face photographic images and any comparable images.
   If the Data being provided is coded, the Provider will not release, and the Recipient will not request, the key to the code.

5. Recipient will not use the Data, either alone or in concert with any other information, to make any effort to identify or contact individuals who are or may be the sources of Data without specific written approval from Provider and appropriate Institutional Review Board approval, if required pursuant to 45 CFR 46. Should Recipient inadvertently receive identifiable information or otherwise identify a subject, Recipient shall promptly notify Provider and follow Provider's reasonable written instructions, which may include return or destruction of the identifiable information.

6. By signing this Agreement, Recipient provides assurance that relevant institutional policies and applicable federal, state, or local laws and regulations (if any) have been followed, including the completion of any IRB or ethics review or approval that may be required.

7. The parties agree to take such action as is necessary to amend this Agreement, from time to time, in order for the Provider to remain in compliance with the requirements of HIPAA.

Agreement ID: AGR00025510

Attachment 3
Data Transfer and Use Agreement
Identification of Permitted Collaborators (if any)

For all purposes of this Agreement, the definition of "Collaborator Personnel" checked below will pertain:

☐ "Collaborator Personnel" means: None. No collaborators are permitted on the Project.

-OR-

☑ "Collaborator Personnel" means as set forth below and agreed upon between the Parties:
"Collaborator Personnel" means: faculty, employees, fellows, or students of an academic institution, which institution (i) has agreed to collaborate in the Project, (ii) has faculty, employees, fellows, or students who have a need to use or provide a service in respect of the Data in connection with its collaboration in the Project, and (iii) has executed an agreement that is substantially similar to this Agreement.