

**Socio-ecological risk factors, explanatory models and treatment-seeking behaviours associated with Mseleni Joint Disease:
A biocultural mixed methods study**

BY

ELIZABETH SARAH DINKELE

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SUPERVISOR: ASSOCIATE PROFESSOR VICTORIA E. GIBBON
CO-SUPERVISOR: DR ROBEA BALLO

Plagiarism declaration

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Abbreviations

CI- Confidence interval

COVID-19- Coronavirus disease of 2019

GPS- Global positioning system

HIV- Human immunodeficiency virus

MED- Multiple epiphyseal dysplasia

MJD- Mseleni joint disease

NSAIDs- Nonsteroidal anti-inflammatory drugs

OA-Osteoarthritis

OPD-Outpatients department

OR- Odds ratio

SA-South Africa

SABP-Southern African Bantu-speakers

TAM- traditional African healing/medicine

TB-Tuberculosis

WBM- Western biomedicine

ICD-10 - International Statistical Classification of Diseases and Related Health Problems 10th Version

Abstract

Mseleni Joint Disease (MJD) is a crippling osteoarthropathy of unknown aetiology endemic to southern African Bantu-language speakers in a remote region of Northern KwaZulu-Natal, South Africa. Effective management of MJD has been hindered by limited insight into risk factors, explanatory models or treatment-seeking behaviours in those affected. Until MJD is better understood, disability, unemployment and dependence on social assistance grants and family income for subsistence will remain a reality for those affected. A mixed methods study was conducted with the aims of examining risk factors, explanatory models and treatment-seeking behaviours associated with MJD. The distribution, differential diagnosis and treatment of MJD were statistically analysed using medical records ($n=723$), MJD-patient surveys ($n=37$) and a meta-analysis. Socio-economic and cultural risk factors were assessed from surveys ($n=99$) and census publications. Interviews with MJD patients ($n=6$), nurses ($n=7$) and doctors ($n=9$) were qualitatively analysed for themes pertaining to perceptions, experiences and treatment-seeking for MJD. A point prevalence of 9% was estimated. Women were nearly twice as likely to have MJD than men (OR= 1.89; $p=0.03$) and the likelihood of MJD increased almost three-fold in those older than 50 years (OR= 2.83; $p<0.01$). Age was a confounder of the association between gender and MJD, as the sample was skewed in the representation of elderly women. MJD was only detected in patients older than 35 years, indicative of a later onset age than previously reported. The prevalence of MJD in settlements along tar and concrete roads, with access to public transport but limited piped water was suggestive of environmental risk factors or differential access to hospital-based care. Explanatory models of MJD were supernatural (witchcraft or ancestral displeasure); natural (nutritional deficiencies, 'genetics' and/or environmental); and/or social (gender-based practices and lifestyle). MJD patients described supernatural and natural aetiologies, and conceptualised disability as an inevitable reality. Consequently, patients reported taking few measures to prevent joint immobility, focussing instead on immediate symptomatic relief. Psychosocial and systemic barriers to treatment were suggestive of a disconnect between traditional African healing and Western biomedicine. This work demonstrates the value of the biocultural approach in identifying spatial, ecological, social and cultural processes that shape population patterns of health and disease.

Chapter 1: Background

Mseleni Joint Disease (MJD) is a crippling musculoskeletal disease of unknown aetiology that is geographically localised to a remote group of Southern African Bantu-language speaking people in Northern KwaZulu-Natal, South Africa (Wittman & Fellingham, 1970). This disease has been described as a bilateral, uniform, complex osteoarthropathy that is most severely localised to the hip region (Wittman & Fellingham, 1970). The precocious onset of MJD reported in young children and adolescents is alarming as this condition is progressively degenerative, inevitably leading to widespread joint degeneration, chronic pain and disability in adulthood (Fellingham *et al.*, 1973; Mann & Fredlund, 1988; Waller, 1998). As MJD progresses, those affected lose the ability to perform everyday activities independently (Mann & Fredlund, 1988; Waller, 1998). This inevitably leads to increased reliance on personal care from family, friends or neighbours and financial dependence on social assistance grants and family sources of income (Mann & Fredlund, 1988; Waller, 1998). While limited schooling is common in children and adolescents in the region affected by MJD, school attendance is more detrimentally affected in MJD-affected households (59% of children), compared to unaffected households (38% of children) (Mann, 1984). Insight into risk factors, perceptions of MJD and the care-needs of affected individuals is needed to formulate care strategies that mitigate the burden of MJD on individuals, families, local communities and the regional healthcare system.

Despite extensive research no anatomical (Lockitch *et al.*, 1973a; Lockitch, 1974; Solomon *et al.*, 1986; Agarwal *et al.*, 1997), molecular (Sokoloff *et al.*, 1985; Changlong *et al.*, 1987; Schnitzler *et al.*, 1987; Ballo, 1998), genetic (Lockitch, 1974; Nurse *et al.*, 1974; Beighton, 1992; Ballo *et al.*, 1996), or environmental causes of MJD have been identified (Burger *et al.*, 1973; Fellingham *et al.*, 1973; Lubbe, 1973; Lockitch, 1974; Mackenzie, 1981; Mann, 1984; Yach & Botha, 1985; Fincham *et al.*, 1986; Marasas & Van Rensburg, 1986; McLaren *et al.*, 1987; Viljoen *et al.*, 1993; McGlashan *et al.*, 1997; Ceruti *et al.*, 2003). This has led to the proposal that the aetiology of MJD is complex and multifactorial -comprising environmental and epigenetic (and perhaps genetic) factors (Ballo, 1998; Gibbon *et al.*, 2010). Gibbon and colleagues (2010) cited the geographic localisation of MJD and familial clustering of disease with the apparent lack of Mendelian inheritance in favour of an epigenetic cause in response to environmental stimuli.

The biocultural approach has been used in biological anthropology since the mid-twentieth century to characterise complex diseases with multifactorial causes (Leurs, 2010; Himmelgreen, 2013; Himmelgreen *et al.*, 2014; Mushrif-Tripathy, 2014; Risso *et al.*, 2017; Shattuck, 2019). This approach is predicated on the concept that humans are both biological and cultural beings, and interactions between people and their physical, social and cultural environments are dynamic and dialectic (McElroy, 1990; Khongsdier, 2007; Leatherman & Goodman, 2011). The strength of the biocultural approach is that information pertaining to demographics, public health, medicine, biology, ecology, and

geological science can be operationalised and integrated in a single study on risk factors of a disease. Identifying biological, cultural and ecological risk factors requires accurate and up-to-date data on the distribution of MJD, and local conditions in the affected region. The paucity of epidemiological data on MJD is noteworthy as the last prevalence surveys were conducted in 1973, 1985 and 1987 (Fellingham *et al.*, 1973; Yach & Botha, 1985; McLaren *et al.*, 1987). Since then, the sociocultural, economic and environmental landscape has changed drastically in the region (Bateman, 2000; Gibbon *et al.*, 2010; Hazell, 2010). It is expected that if aspects of the local environment are aetiological of MJD, then widespread changes in the social, economic and ecological milieu in the region are likely to be reflected in the distribution and prevalence of this disease (Gibbon *et al.*, 2010; Dinkele *et al.*, 2020). Measuring the distribution of MJD is central to identifying risk factors so that healthcare interventions can be informed by past trends and current requirements of those affected.

Social and cultural contexts shape how diseases are conceptualised, and how responses to illnesses are conditioned (McElroy, 1990; Leatherman & Goodman, 2011). While the social and cultural context of MJD has been explored (Lubbe, 1973; Lockitch, 1974; Du Toit, 1979; Mann, 1984; Waller, 1998; Hazell, 2010), little is known about explanatory models and treatment-seeking behaviours in people with MJD. Explanatory models of diseases refer to ways that individuals understand and explain illnesses, and these may differ between patients, their families and healthcare providers (for example, doctors and nurses). Interactions between healthcare providers and patients are shaped by the linguistics, sociocultural backgrounds, education and belief systems (Kleinman *et al.*, 1978). Biomedical healthcare providers assess diseases from a lens shaped by their training as doctors, nurses or therapists and attempt to provide care that takes the patient's culture and context into account (Kleinman *et al.*, 1978). Similarly, in patients, appraisals of symptoms, assumptions about causation, and responses to medical advice are conditioned by their level of education and schooling and their cultural, familial, local and treatment context (Uskul, 2010). Cogent evidence suggests that sociocultural contexts impact disease presentation and treatment-seeking behaviours (Niu *et al.*, 2011; Rowley *et al.*, 2016; Kahissay *et al.*, 2017; Mchunu *et al.*, 2019). For many southern African Bantu-language speaking people in South Africa, explanatory models of diseases are shaped by beliefs about traditional African medicine and Western biomedicine (Washington, 2010). Treatment-seeking behaviours are generally influenced by beliefs (and knowledge) surrounding the aetiology, associated symptoms, perceptions of healing, consequences of disease and the degree of trust the patient has for the physician and healthcare system (Uskul, 2010). Cross-cultural studies in illness representations point to clear differences in the formation of beliefs regarding disease causation, treatment and consequences (Niu *et al.*, 2011; Rowley *et al.*, 2016; Kahissay *et al.*, 2017; Mchunu *et al.*, 2019). In traditional African medicine, collectivism is integral in shaping health perceptions, as illnesses have metaphysical causes and health and healing requires living harmoniously with one's community, environment, family, ancestors and body (Uskul, 2010; Kanu, 2013). This differs from western

biomedicine, which is dominated by empiricism, rationalism and individualism, as diseases, their causes and treatments are not understood as spiritual but physical entities (Uskul, 2010). Despite notable differences between knowledge systems and practices between western biomedicine and traditional African medicine- both systems are used by patients in the MJD affected area (Lockitch, 1974; De Wet & Ngubane, 2014; Nciki, 2015; Nzimande *et al.*, 2021). Insight into how MJD is understood and experienced by healthcare providers and people with MJD is needed to understand the extent to which patients use both types of healthcare.

Developing countries like South Africa are grappling with a double burden of communicable and non-communicable diseases, with the latter estimated to lead to an increase in mortality of 60% by 2030 (Global Burden of Disease (GBD) Country Collaboration, 2013). In light of these projections, and the burden on the healthcare and social assistance systems, determining risk factors of MJD is a matter of priority (Massyn *et al.*, 2020). A biocultural approach is utilised in the present study to assess risk factors, explanatory models and treatment-seeking behaviours associated with MJD. To provide context for this research, the literature pertaining to MJD is reviewed below, and the theoretical framework, aims and objectives are presented. Components of this section have been published as a commentary in *Lancet Rheumatology* (Appendix A1) and will be referenced where relevant (Dinkele *et al.* 2020).

1.1 A note on terminology

At the outset of this thesis the author seeks to clarify and define several terms that are critical to this study. The population-at-risk of MJD will be referred to as indigenous Southern African Bantu-language speaking people (SABP) from the uMkhanyakude region in KwaZulu-Natal (South Africa), to the exclusion of indigenous San and Khoekhoe people. The term “Bantu” has several socio-political connotations in South Africa due to its use by the apartheid government (1910-1990) in discriminatory policies against SABP people (Tawha *et al.*, 2020). Many inhabitants of South Africa are descendants of Bantu-language speakers who migrated eastwards, and southwards from West Central Africa more than 2000 years ago (Murdock, 1959; de Filippo *et al.*, 2012). Bantu-language speaking people are representative of 300-600 ethnic groups throughout Africa (Lewis *et al.*, 2009; de Filippo *et al.*, 2012). South Africa is home to two main groups of SABP: the Sotho-Tswana and Nguni, the most widely spoken language is Zulu (an amalgamation of Tonga and Nguni) (Nurse, 1973). The population affected by MJD are of the Zulu-language and culture and will be referred to broadly as SABP.

The terms traditional African healing/medicine (TAM) and Western biomedicine (WBM) will be used when discussing the healing practices used to treat MJD. The World Health Organisation (WHO) defines traditional medicine and healing as “*the sum total of all knowledge and practices, whether explicable or not, used in diagnosing, preventing or eliminating a physical, mental or social disequilibrium and which rely exclusively on past experience and observation handed down from*

generation to generation, verbally or in writing” (WHO, Programme on Traditional Medicine, 2001: 2). TAM includes a variety of healing practices, approaches, knowledge systems pertaining to health, illnesses and diseases that originate in Africa and do not conventionally fall within the confines of WBM (Sobiecki, 2014). Central to WBM is the belief that diseases are the result of disruptions to standard functions in different parts of the body, as a result, diseases are generally restricted to biological, chemical and physical phenomena (Craffert, 1997). Various countries and cultures have traditional healing systems that appear and function differently as they are not based on a series of shared beliefs like WBM (Ashforth, 2005; Edwards, 2010). Traditional healing practices across the world are dynamic and variable due to the unique geographic, cultural and agricultural systems wherein they exist (Ashforth, 2005; Pemunta & Tabenyang, 2020b). In this thesis, unless otherwise stated, TAM will be used to refer to healing practices in SABP people. While there are differences in beliefs, and cultural practices in SABP, ideas surrounding health, wellness and disease in these groups traditionally revolve around land, community, ancestors, nature and the individual’s connection to these elements in a deep and profound manner (Conco, 1972; Ashforth, 2005; Washington, 2010; Mokgobi, 2014; Sobiecki, 2014; Pemunta & Tabenyang, 2020b). The complex relationship that exists between WBM and TAM in SA will be detailed in Section 1.8.

1.2 A brief history of MJD

The first accounts of MJD are from local oral histories that trace the advent of this disease to the early 1900’s (Lockitch, 1974; Theron, 1975). The first written accounts are from missionaries who noted a mysterious hip disease suspected to be a form of rheumatism that dwarfed and crippled many local people residing near the Mseleni Mission Station (Theron, 1975). The condition which was known to locals as “*Isindulo*” or “*Unyonga*” (meaning a disease affecting the joints), earned the name MJD in medical circles due to the localisation of sufferers around the Mseleni Mission Station which later became the Mseleni Hospital (Fredlund, 2003). Local explanations of MJD stemmed from the understanding that ill health and diseases were the result of conflict or disharmony with one’s land, community and/or ancestors (Mann, 1984). As a result, people with MJD primarily sought care from diviners (*isangomas*) and traditional healers (*inyangas*) to restore spiritual, environmental and social balance and health (Theron, 1975; Waller, 1998).

Biomedical services in the area were limited in the first half of the century (Fredlund, 2003). The arrival of missionaries (1906), the establishment of the Mseleni nursing station (1936), and the instalment of a fulltime physician Dr Vos (1950) led to the penetrance of WBM in the area and the establishment of the Mseleni Hospital in 1859 (Fredlund, 2003). Upon his arrival, Dr Vos found the area heavily burdened by malaria (Fredlund, 2003), bilharzia (Cooppan *et al.*, 1986) and diarrheal diseases (Grant & Fredlund, 1995). A mysterious joint disease disabling locals caught the interest of Dr Vos who informed the Head of Medical Statistics and Epidemiology at the South African Medical

Research Council of South Africa in Pretoria (Fredlund, 2003). Thereafter, two epidemiologists, Wittman and Fellingham (1970) were assigned to investigate this condition. In preliminary surveys, an alarming prevalence of 66% in women and 25% in men residing near to the Mseleni Hospital was detected (Wittman & Fellingham, 1970). Of particular concern was the initiation of joint pain in young children and adolescents, which appeared to progress into physical disability by adulthood (Wittman & Fellingham, 1970). Prevalence figures of this magnitude indicated a regional crisis, which initiated several investigations to characterise the pathology, distribution and aetiology of this disease (Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985; McLaren *et al.*, 1987). In the years that followed several social, cultural, environmental, biological and genetic factors were investigated as possible causes of MJD, yet no conclusive answers were found (Burger *et al.*, 1973; Fellingham *et al.*, 1973; Lockitch *et al.*, 1973a; Lubbe, 1973; Lockitch, 1974; Nurse *et al.*, 1974; Mackenzie, 1981; Mann, 1984; Sokoloff *et al.*, 1985; Yach & Botha, 1985; Fincham *et al.*, 1986; Marasas & Van Rensburg, 1986; Solomon *et al.*, 1986; Changlong *et al.*, 1987; McLaren *et al.*, 1987; Schnitzler *et al.*, 1987; Beighton, 1992; Viljoen *et al.*, 1993; Ballo *et al.*, 1996; Agarwal *et al.*, 1997; McGlashan *et al.*, 1997; Ceruti *et al.*, 2003; Fredlund, 2003).

1.3 Differential diagnosis and onset of MJD

MJD has been described as a bilateral, uniform osteoarthropathy that is most severely localised to the hip region (Lockitch *et al.*, 1973a; Agarwal *et al.*, 1997). The pathogenesis of MJD is poorly understood because the onset appears to be largely asymptomatic, absent of swelling, inflammation or systemic complications (Agarwal *et al.*, 1997). Lockitch (1974) conducted a clinical survey and found the onset of MJD in lower limb joints, specifically the hips, knees and ankles. This was supported by Du Toit (1979) who identified ankle pain, stiffness and limping as the first symptoms of MJD for 16% of women and 55% of men. The first symptoms of MJD are crepitus, joint pain and stiffness, which are not generally cause for concern in a region where physical labour is commonplace (Agarwal *et al.*, 1997). The onset age of MJD is variable as several patients report experiencing onset in childhood and adolescence, and numerous women report the onset subsequent to the birth of their first child (Lockitch, 1974). The peak onset for females is suspected to be 40-50 years-of-age (Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985). Yach & Botha (1985) reported a decrease in the incidence of MJD in adolescents and children, suggesting that a change in onset age may suggest MJD exclusively affected an age-cohort, and that perhaps exposure to a causative factor was generational.

Pain, stiffness and crepitus in hip joints has been reported in 80% of MJD patients under 15 years-of-age, despite the absence of radiographic evidence of joint irregularities (Du Toit, 1979). While some irregularities in the structure and shape of the femoral head, acetabulum and ischiopubic ramus have been identified in adolescents with MJD, these were largely asymptomatic (Lockitch, 1974; Du Toit, 1979). These changes are likely to be the first indication of MJD, before arthritic changes like

osteophytosis, reduced bone mineral density and more severe shape deformities occur (Du Toit, 1979). Solomon (1986) suggested the localisation of MJD to the pelvic region may be linked to mechanical stress on the developing triradiate cartilage as a result of daily activities requiring the carrying of heavy loads. Radiographic evidence of MJD includes large inter-articular spaces, subarticular sclerosis and osteophytes (Figure 1.1A), in addition to a combination of skeletal deformities such as protrusio acetabuli, multiple epiphyseal dysplasia (MED), and flattening or so-called mushrooming of the femoral head with subluxation (Figure 1.1B) (Lockitch, 1974; Du Toit, 1979; Solomon *et al.*, 1986; Agarwal *et al.*, 1997). Another common feature of MJD is the incidence of severe lumbar lordosis (inward curvature of the lumbar spine) in patients with advanced pathology (Lockitch *et al.*, 1973a; Agarwal *et al.*, 1997). While pronounced lumbar lordosis is common in SABP people, it is usually asymptomatic (Adebajo & Davis, 1994). Patients with MJD tend to adopt a shuffling gait as cartilage breakdown in the pelvis limits flexion of the femur, and results in a reliance on walking aids (Lockitch, 1974). The resultant lumbar flexion and shuffling are likely to place additional strain on the spinal region, and thus spinal pathology may be a secondary symptom caused by altered gait.

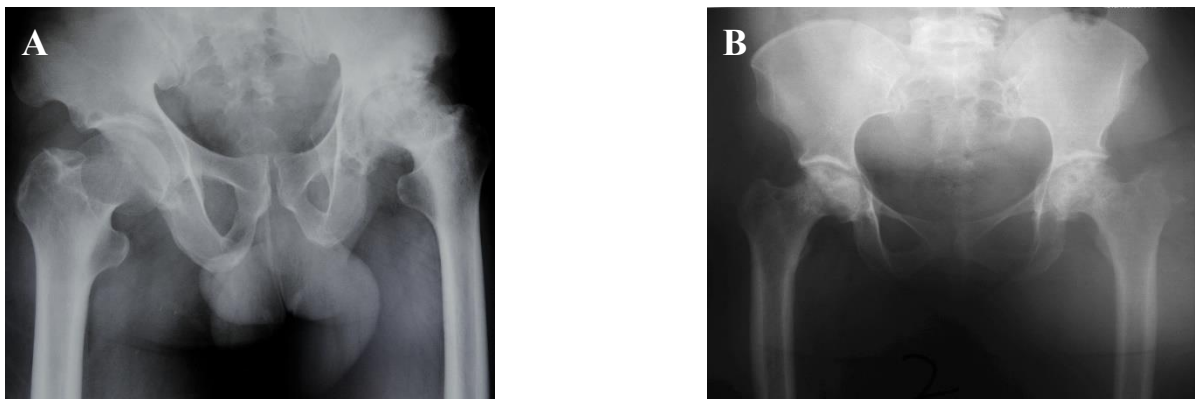


Figure 1.1 Radiographs showing hip pathology characteristic of Mseleni Joint Disease (MJD). (A) Bilateral hip dysplasia, with subchondral cysts and femoral head flattening (more severe on the right) in a man with MJD. (B) Bilateral hip arthrosis with protrusio acetabuli and femoral head cyst, ovoid deformity leading to severe restriction of abduction, adduction and rotation in a woman with MJD. [Radiographs sourced from medical records at the Mseleni Hospital (HREC: 079/2019). Pathology described by V Fredlund, personal communication 2019, August 8th].

1.3.1 Protrusio acetabuli, MED and brachydactylous dwarfism

The incidence of MJD in the hip joint is surprising given that hip OA occurs half as frequently in SABP compared to of European or Asian descent South Africans (Beighton & Solomon, 1981). The high prevalence of protrusio acetabuli and MED in individuals with MJD has led to the suggestion that these may be a predisposing factor for pelvic arthropathies (Beighton & Solomon, 1981). This was further expounded by Solomon *et al.* (1986) who proposed different subtypes of MJD characterised by: protrusio acetabuli, MED and brachydactylous dwarfism. This hypothesis is not widely accepted as it fails to account for (1) the incidence of MED and protrusio acetabuli in other conditions with variable aetiologies, (2) the co-occurrence of MED and protrusio acetabuli in some MJD patients, and (3) the

asymptomatic occurrence of these morphologies in asymptomatic individuals (Sokoloff *et al.*, 1985; Adebajo & Davis, 1994; Agarwal *et al.*, 1997; Fredlund, 2003).

Protrusio acetabuli is characterised by deformity of the medial wall of the acetabulum associated with medial migration of the femoral head into the pelvic cavity (Chueire *et al.*, 2002). Primary protrusio acetabuli is a diagnosis reserved for patients in whom no genetic causative factors can be identified (McBride *et al.*, 2001). Primary protrusio generally develops due to stress during childhood that causes irregularities in the structure and function of the fibrocartilaginous acetabular labrum during development (Alexander, 1965). Secondary protrusio is attributable to underlying conditions like rheumatoid arthritis, gout (McBride *et al.*, 2001) and perhaps MJD. Secondary protrusio can have inflammatory (*e.g.* rheumatoid arthritis or psoriatic arthritis) or noninflammatory causes (*i.e.* a metabolic, neoplastic, or connective-tissue abnormality) (McBride *et al.*, 2001). Inflammatory causes lead to destruction and weakening of the bone surrounding the hip with resultant migration along the joint-reaction vector (all the forces crossing the joint that must be present to produce motion) (McBride *et al.*, 2001). In cases of metabolic or connective tissue causation, a qualitative deficiency of the bone is usually responsible (McBride *et al.*, 2001). The thin medial acetabular wall has less strength than the better supported bone in the superior portion of the femoro-acetabular joint, and when it falls below the threshold of strength required to withstand the medial component of the joint-reaction force, secondary protrusion occurs (McBride *et al.*, 2001). Bilaterally symmetrical protrusio acetabuli is suspected to occur in at least 60% of MJD patients (Du Toit, 1979). The higher frequency of protrusio acetabuli in females with MJD and its correlation with ageing has led to the suggestion that this subtype is caused by environmental and cultural factors (Solomon *et al.*, 1986). These causes are yet to be explored in the population. Solomon and colleagues (1986) hypothesised that the MJD-protrusio acetabuli subtype has an environmental aetiology while the MED subtype has a genetic aetiology.

MED manifests with pain and joint stiffness attributable to irregular ossification (Czarny-Ratajczak *et al.*, 2001). Patients with MED present with short stature, deformity of the legs, and ligamentous laxity (Czarny-Ratajczak *et al.*, 2001). Abnormal epiphyseal morphology in children with MJD led Lockitch *et al.* (1973a) to suggest MED may be associated with the disabling arthrosis seen in MJD affected people. Similarly, Du Toit (1979) hypothesised that irregularities in the shape and contour of epiphyseal surfaces in younger MJD patients may be linked to degeneration of weightbearing joints that is seen as this condition progresses. MED has been linked to aberrations in genes encoding extracellular matrix components (Muragaki *et al.*, 1996; Czarny-Ratajczak *et al.*, 2001). A study by Ballo (1998) into familial osteoarthropathies in SA found no association between MJD and several genes previously implicated in extracellular matrix composition in patients with MED.

A number of individuals with an unusual dwarfing dysplasia called brachydactylous dwarfism have been identified in the MJD-affected region (Lockitch *et al.*, 1973b; Du Toit, 1979; Viljoen *et al.*, 1993). This dwarfing phenotype is rare, occurring in less than 0.1% of the population in the region

(Viljoen *et al.*, 1993). This mild form of dwarfism is associated with marked epiphyseal dysplasia of the hips, knees, ankles, flared epiphyses and short, thick metacarpals and metatarsals (Du Toit, 1979). Clinical and radiological data suggest brachydactylous dwarfism in the Mseleni region falls within the range of spondyloepiphyseal dysplasia due to the involvement of epiphyses and vertebral bodies (Lockitch *et al.*, 1973b). Beighton (1984) noted that dwarfed individuals were mostly members of affected families which led to the suggestion that the dwarfism phenotype represents the end of the spectrum of severity of MJD. The incidence of stunted long bone growth and epiphyseal dysplasia in MJD patients has been cited as evidence that MJD is a more severe form of brachydactylous dwarfism (Viljoen *et al.*, 1993). However, this is negated by the fact that not all dwarfed patients suffer from MJD (Lockitch, 1974; Agarwal *et al.*, 1997). It is notable that various types of dwarfism commonly occur with other endemic OA's like Kashin-Beck disease and Handigodu joint disease (Agarwal *et al.*, 1997). Kashin-Beck disease is endemic to the Tibetan Plateaus in China, Russia and parts of North Korea (Sudre and Mathieu, 2001), where Handigodu is endemic to Karnataka in India (Agarwal *et al.*, 1997). Lockitch *et al.* (1973a) suggests that these conditions are unlikely to be of aetiological significance to MJD, suggesting that clinical and radiological resemblances are superficial. While some have speculated that these diseases and MJD are a single syndrome, this is disputable because Handigodu joint disease has a genetic aetiology and the Kashin-Beck disease is caused by nutritional deficiencies and region-specific fungal contaminants (Du Toit, 1979). Parents of dwarfed individuals tend to be of regular stature, but Viljoen (1993) has suggested that the comorbidity of MJD and BD may be indicative of a causative gene involved in both conditions. Despite efforts to look at the genetic link between BD and MJD, no common causes have been detected. (Lockitch, 1974; Viljoen *et al.*, 1993).

1.3.2 Pathophysiology

Little is known about the physiological processes underlying the pathology of MJD. Defective extracellular matrix formation, dysregulated bone mineralisation and resorption have been identified in histological analyses of joint biopsies from MJD patients (Schnitzler *et al.*, 1988). Sweet *et al.* (1987) investigated the morphology of hyaline cartilage in MJD patients and detected significant amounts of smaller non-aggregating proteoglycans compared to samples from healthy joints and those with osteoarthritis (OA). As matrix factors do not function in isolation, but interact with circulating cytokines and growth factors, any alterations in these molecular pathways, may ultimately lead to disease pathology (Gibbon *et al.*, 2010).

1.4 Environmental conditions and lifeways in the MJD-affected region

The warm, subtropical climate in the MJD affected region is similar to other regions along the KwaZulu coastline as summers are hot and humid (average temperatures of 29°C), while winters are cool and dry (average temperatures of 17°C) (Ceruti, 1999). The most rainfall in the region occurs during the summer months, approximately 1100mm per annum (Tinley & Van Riet, 1981). The water in the area is generally sourced from either one of the freshwater lakes (Figure 1.2A), small rivers or boreholes/pits dug into the sandy aquifer upon which the inhabitants live. The mission hospital also pumps and purifies water from Lake Sibaya into a reservoir and then on to a series of taps in the vicinity (Pooley, 1996).

The region is geologically characterised by longitudinal landforms parallel to the coastline that form unique ecological zones with distinct biotic and climatic characteristics (Pooley, 1996). These zones are the sand forest zone, palm zone, coastal lake zone and coastal zone (Figure 1.2A) (Pooley, 1996). The Mseleni settlement lies within the sand forest zone, which is characterised by subtropical forests occurring on ancient sand dunes (Pooley, 1996; Ceruti *et al.*, 2003). The indigenous vegetation is predominantly a mixture of treeless grasslands and a savanna forest which support a diversity of animal and plant species (Tinley & Van Riet, 1981; Ceruti, 1999). The vegetation is well-adapted for growth in grey-white, sandy soil that is deficient in extractable nitrogen, phosphorus, potassium, calcium, zinc and boron (Ceruti, 1999). The sand forest zone is an important resource to locals, as it provides building materials, traditional medicines and several edible plants (Pooley, 1996). The ecological environment influences the resources that are available to locals and the local lifeways in the region.

1.4.1 The socio-political context

The uMkhanyakude district is divided into different communities falling under the rule of Zulu chiefs or *amakosi* who have appointed *izindunas* or headmen to govern each ward or *izigodi* and ensure the needs of their people are met (Mann, 1984; Hazell, 2010). Umhlabuyalingana is largely managed by the Ingonyama Trust, which manages land allocation, and the interests of the people and communities residing in this region. Mseleni is the collective name for the *izigodi* surrounding the Mseleni hospital which falls under the Mabaso Tribal Authority. Mseleni is at the intersection of several municipal boundaries, which do not map neatly onto *izigodi* boundaries, but are essential for municipal governments to plan service delivery (Umhlabuyalingana Local Municipality. 2018: 3).

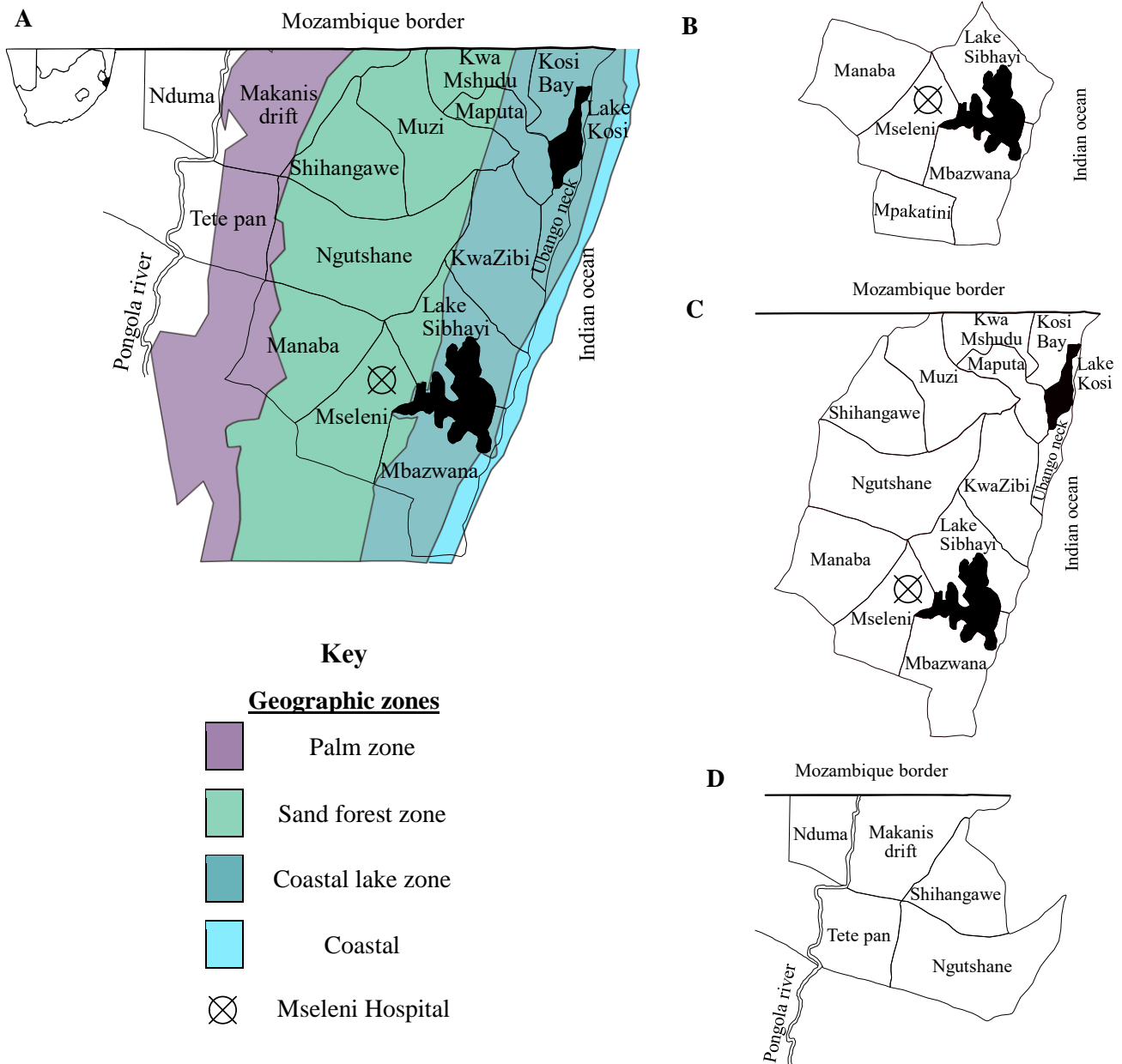


Figure 1.2 Maps of the region affected by Mseleni Joint Disease (MJD) in Northern KwaZulu-Natal, South Africa. (A) Geographic zones mapped onto geographic areas surveyed in the MJD-affected region. Areas surveyed in the three prevalence surveys by (B) Fellingham *et al.* (1973), (C) Yach & Botha (1985) and (D) McLaren *et al.* (1987).

The population residing in the MJD-affected area are largely of SABP of Zulu language and culture (Mann & Fredlund, 1988). The word Zulu means God’s people or people of heaven/the sky and implicit in the name is the belief that the Zulu are a divine people (Washington, 2010). Traditional beliefs, values and cosmologies of SABP people are dominant in the region as *umhlaba* (world/soil), *umhakathi* (community), *isintu* (culture) and *ingqikithi* (the soul) are profoundly linked to *uMvelinqangi* (God or the Creator) and the *amadlozi* (ancestors) (Washington, 2010). Since the arrival of Christian missionaries in the region (1906), cosmologies have become

pluralistic incorporating components of western Christianity and traditional African worldviews (Edwards, 2011). This has had a significant impact on social dynamics and healing practices in the region, which will be explored in the latter part of this chapter.

Locals largely reside in kraals, which consist of a homestead occupied by a family usually consisting of a man, his several wives and their children (Fellingham *et al.*, 1973; Yach & Botha, 1985). Practices like polygamy remain commonplace with several men marrying multiple women when they are can afford to pay *lobola* ('bride price') (Rangan & Gilmartin, 2002; Hazell, 2010). Social structures are largely patriarchal as household heads are usually male and most decisions are deferred to men, even if they spend extensive periods away from home due to circular migration (Rangan & Gilmartin, 2002). Women traditionally retain the responsibility of crop cultivation, household management, childcare and provision of food and water (Fredlund, 2003). Culture is dynamic, however, as the proportion of women heading households has increased significantly in rural regions in SA (Rangan & Gilmartin, 2002).

1.4.2 The socio-economic context and household subsistence

Subsistence farming, gathering and monetary income are critical to the regional economy (Mann & Fredlund, 1988). Locals often grow maize, peanuts and cassava in their gardens, and those near rivers or lakes also grow sweet potatoes, amadumbi, cabbage, spinach, tomatoes and pumpkins (Lubbe, 1973). Crop yield is poor due to the lack of soil nutrients, limited use of fertiliser and frequent droughts (Mann, 1984). Cultivation is done by hand or an ox plough (Mann & Fredlund, 1988), and livestock are considered assets in the region. Cattle and goats are kept for sale and/or slaughter on special occasions (Hazell, 2010) and chickens are an important source of protein and monetary income (Hazell, 2010). Diets are supplemented with wild fruits, nuts and *imifino* (leafy vegetables) that are locally foraged if time and weather permit (Fredlund, 2003). Gathering dry wood for cooking from nearby forests is common in households with limited access to gas or electricity (Hazell, 2010).

While gathering and farming were largely favoured prior to democracy in SA (1994), these have become secondary to reliance on monetary income and store purchased food (Mann & Fredlund, 1988; Hazell, 2010, Umhlabuyalingana Local Municipality, 2021: 136). Entrepreneurial locals brew and sell homemade beer, collect and deliver water, produce baskets and grass mats, and sell medicinal plants and herbs as sources of income (Hazell, 2010). Apart from hospitals, schools and stores in the region, forestry plantations at Manzengwenya and Mbazwana are the most significant employers of locals (Mann & Fredlund, 1988). As there are few work opportunities in the region, many young, able-bodied people become circular migrants, travelling to more densely populated cities for employment opportunities, and returning seasonally with income, or permanently due to old-age or illnesses (Mann, 1984; Collinson *et al.*, 2006). Only 3% of the economically active population in the municipality earns

more than R1 600 per month, and unemployment and poverty are common in the region (Umhlabuyalingana Local Municipality, 2017: 36).

Reports suggest improved access to basic amenities like water, sanitation, housing and electricity in the MJD-affected region since the end of apartheid (1994) (Umhlabuyalingana Local Municipality, 2021:136). Despite these improvements, only 19% of locals have electricity, 2% have piped water inside their dwellings and 1% have flushing toilets connected to sewerage systems suggesting poverty is widespread in the region (Umhlabuyalingana Local Municipality, 2021: 137). Only 22% reside in formal dwellings, built with bricks, concrete blocks and corrugated iron rooftops, (Umhlabuyalingana Local Municipality, 2021: 137) with the remainder living in more traditional "beehive" or "wattle and daub" structures built from grass, reeds and mud (Mann & Fredlund, 1988).

Before the roll out of government funded water schemes from 2008-2018, locals frequently travelled several kilometres to rivers, boreholes, pit wells and communal taps to collect water carried by head or hand (Mann & Fredlund, 1988; Grant & Fredlund, 1995). The longevity of these water schemes has been called into question as many people still travel far distances to collect water (Hazell, 2010). Some women and children reportedly walk more than 10km to reach water sources and return with water-laden buckets or barrels (approximately 5-10 litres) carried by hand, head or shoulder. Larger drums (25-125 litres) are used more commonly to prevent multiple trips a day (Hazell, 2010). The relationship between the changing socio-economic environments, local lifeways and distribution of MJD is yet to be assessed.

1.4.3 Socio-economic impact

The outdated information on the prevalence and aetiology of MJD are concerning given the burgeoning unemployment and physical disability rates in the MJD-affected region (Umhlabuyalingana Local Municipality, 2017: 36; Massyn *et al.*, 2020). The generational impact of MJD on families and the wider community is evident as MJD results in physical disability and reliance on familial care and social assistance grants (Mann & Fredlund, 1988; Dinkele *et al.*, 2020). Patients disabled by MJD, and elderly individuals are more likely to make use of government grants or familial care, due to an inability to farm their own food (Mann & Fredlund, 1988). Disability grants are approximately R1780 (\$125) a month and are frequently used to support extended families (South African Social Security Agency (SASSA), 2021).

The high prevalence of disability and reliance on disability grants has stunted economic growth in the region (Massyn *et al.*, 2020). Approximately 50% of young people between the ages of six and twenty five years-of-age with MJD-affected parents had no formal education, compared with only 30% of children of unaffected parents in the same community (Waller, 1998). This is largely because young people (especially girls due to gender-based labour allocations in families) frequently forgo school to

assist with familial care and household subsistence (Mann & Fredlund, 1988). This imbalance further perpetuates poverty and gender inequality as jobs are highly competitive in the region with limited opportunities for those with minimal education (Umhlabuyalingana Local Municipality, 2017: 36; Dinkele *et al.*, 2020). While some reduction in the social burden of disease has been achieved through community interventions (Waller, 1998), further efforts towards community development, access to social grants and support for families may significantly reduce the socio-economic burden of MJD on the community. Until risk factors and barriers to treatment of MJD are better understood, reducing the burden of disease on the community will be challenging.

1.5 Prevalence and distribution of MJD

MJD exclusively affects individuals from uMkhanyakude (previously referred to Zululand or Maputaland) in KwaZulu-Natal, SA (Figure 1.1). The uMkhanyakude district is subdivided into five local municipalities: Umhlabuyalingana, Jozini, Big Five Hlabisa and Mtubatuba (Umhlabuyalingana Local Municipality, 2021: 23). MJD is most prevalent in the Mseleni region in Umhlabuyalingana but has been detected as far north of the Mozambique border, east of the Ubombo mountain range (bordering Eswatini) and the west of the ancient coastal dunes and Lake Sibhayi (Yach & Botha, 1985; Ceruti, 1999).

The current prevalence of MJD is not known as the last epidemiological surveys were conducted in the 1980's. Surveys of MJD have been cross-sectional and largely population-based (Wittman & Fellingham, 1970; Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985; Mann & Fredlund, 1988), except for one that was both population-and hospital-based (McLaren *et al.*, 1987). These surveys sampled different areas within the MJD-affected region (Figure 1.2 B-D). Population-based surveys assessed prevalence by sampling individuals in kraals or homesteads that were geographically stratified according to malaria control areas (Fellingham *et al.*, 1973; Yach & Botha, 1985; McLaren *et al.*, 1987). Radiographic diagnoses were impractical as the survey areas spanned more than 10 000 km, and therefore fieldworkers diagnosed MJD according to participant-reported symptoms and in some cases, proxy reporting from neighbours or family members when individuals were absent from home during sampling (Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985; McLaren *et al.*, 1987). McLaren and colleagues (1987) were able to confirm diagnoses using radiography and proxy reporting of MJD occurred in 52% of participants. MJD was more prevalent in those interviewed (13% of males, 20% of females), than those assessed through proxy-reporting (3% of males, 6% of females) (McLaren *et al.*, 1987). As MJD patients with severe disability were more likely to be at home during sampling, proxy reporting is suspected to result in a slight underestimate of prevalence rates (Lockitch, 1974; McLaren *et al.*, 1987). These studies were limited in their capacity for causal inferences due to the lack of temporality inherent in cross-sectional study designs (Brennan-

Olsen *et al.*, 2017). Despite the limitations due to sampling strategies, study designs and proxy reporting in studies by Fellingham *et al.* (1973); Lockitch, (1974); Yach & Botha (1985); McLaren *et al.* (1987) – these remain the only available estimates of prevalence and distribution, emphasising the need to re-assess MJD using the municipal demarcations and healthcare infrastructure developed in recent years.

A prevalence of 28% was reported by Fellingham *et al.* (1973) and 5% by Yach and Botha (1985). As both studies employed similar sampling strategies, prevalence differences were hypothesised to indicate declining incidence rates of MJD (Yach & Botha, 1985). Yach and Botha (1985) cited lower age-specific prevalence rates as further evidence of a decline in MJD incidence. Interestingly, surveys conducted prior to 1985 detected MJD in 0.5% (Lockitch, 1974) and 6% (Fellingham *et al.*, 1973) of children under 10 years-of-age, whereas Yach and Botha (1985) found no evidence of MJD in children, which they suggested was further proof of a change in the pattern of disease. Lockitch (1974) found that 13% of respondents reported an MJD onset in adolescence or childhood, while 68% reported onset as middle-aged adults with the peak onset age being 40-60 years for men and 30-50 years for women. The highest prevalence of MJD was in individuals 60-70 years-of-age (Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985). As patients generally seek biomedical care for MJD at the advanced stages of degeneration and disability, little is known about the age, rate or pattern of MJD onset (Yach & Botha, 1985; Waller, 1998).

Women are reportedly affected by MJD at least 3 times more frequently than men (Wittman & Fellingham, 1970; Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985; Mann & Fredlund, 1988). Equal incidences of MJD in gender-groups prior to the age of ten have been reported, after which, more women (32-39%) than men (10-11%) are affected (Fellingham *et al.*, 1973; Yach and Botha, 1981). These findings led to the hypothesis that gender-based differences in lifeways risk factors of MJD (Lockitch, 1974; Yach & Botha, 1985; Gibbon *et al.*, 2010). These will be discussed in more detail in the section on risk factors below.

The geographic localisation of MJD is well reported with the highest prevalence consistently detected around the Mseleni Hospital, and in the Mseleni and Manaba regions (Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985). The clustering of MJD around the Mseleni hospital may be because of the high density of residential settlements around the hospital (Yach & Botha, 1985; Gibbon *et al.*, 2010). Alternatively, it may point to a unique environmental aetiology around the sand forest belt in the region, as few cases have been detected in adjacent environmental zones (Yach & Botha, 1985).

1.6 Risk factors of MJD

In this section, the terms risk factor, cause, and aetiology will be used interchangeably to refer to factors associated with an increased likelihood of MJD. Identifying risk factors is key to understanding causal pathways and managing this disease.

1.6.1 Lifeways and environmental risk factors

1.6.1.1 Gender

The higher prevalence of MJD in women has led to the suggestion that biological and/or sociocultural factors associated with gender are aetiological of this disease (Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985; Gibbon *et al.*, 2010). Several researchers have proposed that this result may reflect sampling bias, in the form of under-sampling males who were generally absent from the region during sampling due to circular migration in response to employment in cities (Fellingham *et al.*, 1973; Yach & Botha, 1985). Lockitch (1974) also noted that men were also less likely to participate in surveys as they reportedly believed participation may result in hospitalisation. If environmental factors are causes of MJD, the lower prevalence in men may indicate that circular migrants do not experience the same magnitude or duration of exposure to determinants due to prolonged absence from the area (Yach & Botha, 1985; Gibbon *et al.*, 2010).

Prevalence differences between men and women may be attributable to gender-linked sociocultural practices (Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985). Lockitch *et al.* (1973b) has suggested increased loadbearing activities in women and discrepancies in environmental exposures may be risk factors of MJD. Similar to other rural SABP communities, labour allocations in families are gendered as women traditionally retain the responsibility of crop cultivation, household management, childcare and provision of food and water (Fredlund, 2003; Hazell, 2010). In contrast, men usually have more sedentary roles, occasionally partaking in tribal governance, herding cattle or harvesting lala palm to produce palm wine (Lockitch, 1974; Mann, 1984). Labour-intensive activities performed by women in the area, have been hypothesised as a risk factor of MJD women (Lockitch, 1974; Yach & Botha, 1985). Over 8.1% of women diagnosed with MJD were unable to walk without aid, compared to only 1.7% of men, suggesting the possibility of a more severe or rapid onset in women (Yach & Botha, 1985). The severe pathology in women may be further evidence that lifestyle and labour practices are risk factors of MJD, but it may also suggest gender-based differences in survey participation and pursuing healthcare. The last decade has seen many advances to the infrastructure of the area including increased availability of food stores, increased access to transportation (more busses and minibus taxis), a formalised road system and the installation of community and household taps (Umhlabuyalingana Local Municipality, 2021: 33; Hazell, 2010). If gender-linked sociocultural

practices are aetiological of MJD, then changes in these practices may be associated with variations in the demographic distribution.

1.6.1.2 Age

The higher frequency of MJD diagnoses in those over sixty years old, identifies age as a risk factor (Fellingham *et al.*, 1973; Yach & Botha, 1985). Whether increased risk associated with age is attributable to cultural practices, biology or sampling bias is yet to be determined. Aging may also be linked to the accumulation of risk factors over an affected individual's lifetime (Woolf & Pflieger, 2003), which may inevitably cause MJD later in life. Yach & Botha (1985) reported a decrease in the incidence of MJD in adolescents and children in 1985 and hypothesised a changing incident age proposing that MJD was a condition affecting an age-cohort or generation exposed to a causative factor. This was also hypothesised by Lockitch *et al.* (1973a), who suggested that poor growth and development in MJD patients was linked to a significant famine in the region in the 1920s. While age as a risk factor of MJD may be due to generational exposure to a causative agent, this is yet to be explored.

1.6.1.3 Diet, soil, water sources and environmental toxins

The geographic isolation of MJD has led to the suggestion of environmental aetiology (Wittman & Fellingham, 1970; Fincham, 1986; Gibbon *et al.*, 2010). Studies have extensively investigated the association between MJD and elemental concentrations in locally grown fruit and vegetables (Lubbe, 1973; Marasas & Van Rensburg, 1986; Oliver, 1997), water (Lubbe, 1973), fish (Mackenzie, 1981) and soil (Ceruti, 1999; Ceruti *et al.*, 2003; Botha & Porat, 2007; Porat & Botha, 2008) - yet no significant associations have been identified.

Burger *et al.* (1973) detected deficiencies in alkaline phosphatase, organic phosphates, calcium phosphates in locals to the MJD-affected area. Limited dietary intake of phosphates have been associated with poor development and diminished structural integrity in bones (Bartko *et al.*, 2018). Deficiencies in calcium phosphates have been associated with osteoporosis and dysregulation of joint repair processes (Rude *et al.*, 2009). While these deficiencies may explain some of the pathology seen in MJD patients, the lack of association between improvement in community health due to altered soil, crop and water quality has led to the suggestion that dietary deficiencies are unlikely to contribute significantly to MJD (Ceruti *et al.*, 2003). Assessing the association between altered food sources and the prevalence of MJD may be critical in elucidating dietary and lifestyle risk factors of MJD.

Elemental concentrations at commonly used water sources in the region have been assessed as risk factors of MJD: Lake Sibhayi, the Mseleni river and water pits/boreholes in the sand, (Lubbe, 1973). Higher silica levels and lower sulphate, magnesium, iron and nitrogen concentrations were reported, but no significant associations with MJD were detected (Lubbe, 1973). Until recently, limited access to water was common in the affected area and many locals walked far distances to reach

communal taps, boreholes and rivers (Lubbe, 1973; Hazell, 2010). This repetitive action strains weightbearing joints like the knees, hips, spine, wrists, elbows and shoulders and may contribute to the pathology seen in MJD (Lockitch *et al.*, 1973b).

Toxicants have been assessed as causes of MJD, yet no associations have been detected (Mackenzie, 1981; Mann & Fredlund, 1988). Environmental exposure to dichlorodiphenyltrichloroethane (DDT) spraying for Malaria control in the 1900's has been proposed as a cause of MJD (Mann & Fredlund, 1988). This link is yet to be confirmed in the Mseleni region, however, a weak association between serum levels of DDT metabolites and bone mineral density was detected in a coastal Swedish cohort, leading to the conclusion that exposure to DDT is unlikely to constitute a hazard to bone mineral density and OA (Glynn *et al.*, 2000; Wallin *et al.*, 2005). Exposure to environmental DDT may provide a mechanism to explain epigenetic modifications in cartilage and bone maintenance as hypothesised by Gibbon *et al.* (2010).

1.6.2 Biological risk factors

Several bacterial, fungal and viral agents have been investigated as aetiological of MJD, and no apparent causative relationships have been identified (Lubbe, 1973; Nurse, 1985; Marasas & Van Rensburg, 1986; McGlashan *et al.*, 1997). Nurse (1985) proposed that a pathogen with a long-latency period may cause MJD, however, this is negated by the fact that the incidence and distribution of MJD do not resemble patterns characteristic of infectious diseases (Vos *et al.*, 2020).

1.6.2.1 Autoimmunity

Nurse *et al.* (1974) and Changlong *et al.* (1987) reported the absence of inflammatory indicators and autoimmune antibodies in serum samples from MJD patients. This is worth revisiting, especially as defects in the biosynthesis of COL2A1 and COL6A1 proteins causes these molecules to function as autoantigens in joints, resulting in inflammation and pain (Peschken & Esdaile, 1999). Degenerative molecular processes in cartilage and bone are initiated by inflammatory cytokines and degrading enzymes, which are upregulated in osteoarthritic patients in response to mechanical stimulation (Tetlow *et al.*, 2001). The presence of inflammatory biomarkers in MJD patients, is yet to be confirmed, however, the evidence thus far suggests autoimmune factors are unlikely to be causing this MJD.

1.6.2.2 Genetic and epigenetic factors

A genetic aetiology of MJD has been suggested because this disease is geographically endemic and clusters within families (Lockitch, 1974; Nurse *et al.*, 1974). Serogenetic analyses of blood types, erythrocytic enzymes and haptoglobin provide no evidence that MJD affected individuals are genetically different from other SABP (Nurse *et al.*, 1974). Moreover, Hardy-Weinberg analyses of

gene frequencies suggest this community is neither a genetic subpopulation nor an isolate (Nurse *et al.*, 1974). While familial clustering of MJD has been cited as evidence in favour of a genetic aetiology, no distinct patterns of Mendelian inheritance or genomic imprinting have been identified (Lockitch, 1974; Nurse *et al.*, 1974; Ballo, 1998). Due to the lack of Mendelian inheritance, MJD is considered to be a complex, polygenic condition (Ballo *et al.*, 1996; Gibbon *et al.*, 2010). The last molecular genetic study of MJD was conducted in 1996 before the ease and efficiency of Whole Genome Sequencing with Next Generation Sequencing platforms. Seventeen MJD patients were screened for the presence of haplotypes and single nucleotide polymorphisms (SNPs) in genes coding for cartilage maintenance and development. Despite the fact that the candidate genes had been implicated in several arthropathies, no MJD-specific haplotypes or SNPs were identified (Ballo, 1998). No associations were detected between MJD, and genes involved in collagen development (including *COL2A1*) (Ballo, 1998). A possible correlation between *COL9A1* expression and MJD was detected, with authors suggesting a link to non-inflammatory changes in cartilage (Ballo *et al.*, 1996). Further research is required to understand the morphological impact of an upregulation of *COL9A1* in MJD.

The absence of mutations or polymorphisms in several other collagen, bone and synovium-related genes in MJD suggests genomic differences are unlikely to be disease determinants. The reliability of genome-wide screening and the recent development of next generation sequencing warrants a re-evaluation of these and other candidate genes. Several SNPs located within or near genes implicated in cartilage, bone and synovium degeneration have been identified and associated with several known risk factors of osteoarthritic conditions including hip shape, body-mass index, and bone mineral density (Hochberg *et al.*, 2013). Understanding epigenetic factors involved in the pathogenesis of MJD may be more useful in clarifying disease phenotypes and pharmacological targets. Gibbon *et al.* (2010) suggested that the apparent lack of mendelian inheritance or genetic aberrations in MJD patients supports an epigenetic aetiology in response to environmental stimuli. Changes in the expression of pro-inflammatory cytokines, prostaglandins and extracellular matrix degrading enzymes have been implicated in osteoarthropathies and may be relevant to MJD (Malemud *et al.*, 2003; Mariani *et al.*, 2014). Further research is needed to determine whether changes in gene expression in cartilage, bone and/or synovium tissue are implicated in MJD.

1.7 Treatment and management of MJD

Illnesses and healthcare systems in different societies- whether western, African, traditional or ancient- are closely linked to culture and worldviews (Craffert, 1997). As such, societies have developed their own explanations of health and disease, including diagnostic methods, treatments and remedies (Mokgobi, 2014). In the MJD-affected region, local people use a combination of WBM and TAM to understand and treat diseases (Mann & Fredlund, 1988). As little is known about the TAM used to treat MJD, this section will provide an overview of conceptualisations of health, diseases and healing

common in Zulu culture. The aim of the following section is not to provide an exhaustive discourse on TAM and WBM, but to introduce concepts relating to understanding and treating diseases in both paradigms.

1.7.1 Conceptualisations of illnesses and treatments in TAM and WBM

As humanity has its roots in Africa, with South Africa suspected to be a primary source of early migration, there is an inferential implication about the African origin of all forms of healing (Edwards, 2010). TAM broadly refers to a variety of practices, approaches and knowledge systems that are indigenous to SABP and are applied to maintaining health and healing illnesses (Sobiecki, 2014). Traditional cosmologies (worldviews) are essential to understanding health, illness-related experiences and treatment-seeking behaviours in SABP (Conco, 1972; Mokgobi, 2014; Sobiecki, 2014; Pemunta & Tabenyang, 2020b). In the traditional SABP worldview, causes and treatments of diseases can be both natural and supernatural as the universe comprises mutually interwoven spiritual and physical dimensions (Washington, 2010; Kanu, 2013). In the Zulu culture, being healthy and prosperous requires living in harmony with ones *umhlaba* (world/soil), *umhakathi* (community), *isintu* (culture) and *ingqikithi* (the soul) (Washington, 2010). These are profoundly linked to *uMvelinqangi* (God or the Creator) and the *amadlozi* (ancestors) (Washington, 2010). Ancestral, familial and communal spirituality forms the essential context for TAM in Zulu culture (Edwards, 2010). Classifications and categorisation of conditions in TAM in Zulu are based largely on causation, for example *umkuhlane* refers to illnesses of a natural cause, while *ukufa kwabantu* refers to metaphysical disorders (Washington, 2010). Metaphysical disorders are the result of disturbed social relations with ones ancestors, family and/or community (Washington, 2010). Diseases characterised by painful joints, or edema of the ankles are called *umeqo* and these are caused by stepping over the harmful creation of a sorcerer (Washington, 2010; Mokgobi, 2014). *Umeqo* is treated with *ukucaba* which involves incisions on painful joints to administer *muthi* (traditional medicine) and to allow the “bad blood” to leave the body. Treatments are prescribed in response to symptoms and the impact of the condition on the patient and community (Edwards, 2010; Sobiecki, 2014). Thus, in TAM, conceptualisations of illnesses and their treatments are primarily symptom-focussed, with a secondary emphasis on causation.

WBM is a globally consistent paradigm that has a relatively recent historical development compared to TAM (Valles, 2020). The most influential western healing system prior to WBM was the Hippocratic medical tradition which attributed diseases to an imbalance in the anatomical humours (blood, phlegm, yellow bile, and black bile) (Valles, 2020). WBM emerged during extensive social, cultural and economic transformation and industrialisation in European countries in the early nineteenth century. The disease-orientated WBM system is structurally dominant, placing value on rationalism and empirical knowledge (Edwards, 2010; Valles, 2020). Symptoms are used to confirm diagnoses, prior to the prescription of treatment (Edwards, 2010; Sobiecki, 2014). Modern biomedicine is pre-occupied

with scientific reductionism, which maintains that complex interactions and entities can be broken down into smaller constituents or phenomena (Conco, 1972; Sobiecki, 2014). Within this framework, mechanisms or processes of diseases are reduced to their simplest parts to facilitate healing that targets an affected organ or molecular pathway rather than the entire body. Physiological causes of illness and their treatments are given greater weight and are typically seen as separate from the social and physical environments in which individuals are embedded (Bruce, 2002). Thus, in WBM, conceptualisations of illnesses and their treatments are primarily causation-focussed, with a secondary emphasis on symptom relief.

According to Edwards (2010) an individual's failure to act in an appropriate manner places the entire community at risk of the illness because healing within TAM occurs within the communal context and it is thus the responsibility of family and community to facilitate healing (Washington, 2010). This differs from the individualistic approach of WBM with its emphasis on personal autonomy and privacy, as healing occurs in an individual context (Bruce, 2002). While both the WBM and TAM healers play a vital role in community health, their individualistic and communal orientations, respectively, alter the care dynamics with their patients (Edwards, 2010). Despite obvious differences in the orientation of TAM and WBM, the clinical reality of healthcare in many rural South African communities is pluralistic, as an estimated 72% of SABP of different age categories, education levels and occupations combine both forms of medicine (Edwards, 2010; Washington, 2010; Pemunta & Tabenyang, 2020b). Despite differing approaches to the cause and content of disease, and approaches to healing, these medical systems co-exist in the world of the patient because 'truths' of natural and supernatural explanations of diseases resemble one another in their consequences - illness and healing (Ashforth, 2005; Sobiecki, 2014).

There are generally three main types of healers in TAM practiced in Zulu culture: the *inyanga* (traditional healer or doctor), *isangoma* (diviner) and *umthandazi* (faith healer) (Edwards, 2010). *Izinyanga* (healers) are apprenticed to a practicing healer, usually an older relative that teaches use of massages, steam baths and poultices as well as herbal medicines in a ritual context to heal illnesses (Washington, 2010). *Isangomas* are chosen by the spiritual realm after an *ukuthwasa* (transforming experience) (Washington, 2010). It is during the transforming experience such as a seizure or near-death experience that the person communicates with entities of the spiritual realm to learn where they need to train. Following this, the person goes to study under an accomplished *isangoma* who diagnoses illnesses through communicating with the *amadlozi* (ancestral shades) (Mokgobi, 2014). The advent of the *umthanduzi* or *umprofethi*, is an interesting phenomenon traced to the rise of the African Independent Church movement, which broke away from western orientated missionary churches (Pemunta & Tabenyang, 2020b). It has been argued that many of the traditional priest/diviner/cultural healer roles of the *insongoma* have been taken over by the *umthanduzi* combining traditional African and Christian approaches to illness and healing (Pemunta & Tabenyang, 2020b). The training of healers

in TAM is yet to be formalised and regulated in South Africa, despite the recent emergence of institutions offering training in traditional healing practices.

In WBM, healthcare providers (such as doctors, nurses, physiotherapists and occupational therapists) are taught the knowledge needed to work in their profession and undergo practical training before registering with regulatory body. In SA, doctors, nurses, physiotherapists and occupational therapists obtain qualifications in their fields and undergo clinical training before they are able to register with a regulatory body (Health Professions Council of South Africa (HPCSA) or the South African Nursing Council (SANC) (Ashforth, 2005). The role of the doctor includes diagnosing and identifying a disease, while nurses facilitate doctors and treat the illness (experience of disease) in patients. The emphasis of occupational therapy and physiotherapy is recovering and improving functionality that individuals require in daily activities. As WBM is a global system, the above practitioners are universally trained with the same explanations of illnesses, diagnostics, and treatment. Professional bodies play a critical role in the institutionalisation and regulation of WBM training and practice (Ashforth, 2005).

Internal criticism of TAM has been described as weak due to the lack of formal communications between practitioners (Edwards, 2010). The lack of generalisability between TAM in different regions is cited as a potential shortcoming facilitating integration between TAM and WBM in South Africa (Pemunta & Tabenyang, 2020b). Diagnostic and therapeutic procedures in WBM and TAM vary, however patient interviews are perhaps one of the most significant traditions common to both (Pemunta & Tabenyang, 2020b). Traditional healers or diviners are consulted with the expectation that the cause of the illness can and will be divined, thus while the patient's symptoms are reported to the healer, the healer's focus is expected to identify the disease and determine the method of treatment (Edwards, 2011; Sobiecki, 2014). Thus, while TAM and WBM practitioners work from different theoretical orientations, a significant degree of agreement between diagnosis and treatments implies some common perceptions of the patients problems and needs (Sobiecki, 2014). The invalidation and distortion of the TAM in SA is reflective of colonial attitudes that African knowledge systems and sociocultural practices are primitive and undeveloped (Washington, 2010). Prejudicial views are commonly observed in academic literature relating to the supposed 'unscientific' diagnostics or practice of TAM, and the toxicity issues levelled at traditional medicines (Washington, 2010). Ashforth (2005) argues the disconnect between TAM and WBM is partly attributable to the difficulty in effectively translating and interpreting the nuances of African cultural and language-based descriptions of spiritual medicinal plant use and its effects. Despite their differing origins, orientations and practices, WBM and TAM are dynamic, and have both been affected by modernisation, urbanization and socio-political changes in SA (Edwards, 2011).

Medicines and treatments used in TAM derive their acceptability from oral traditions and histories, as well as experiences of healing in the family and communal context (Sobiecki, 2014). It is

a common fallacy that TAM exclusively involves rituals and traditional spiritual forms of treatment, negating the use of various herbal remedies (Sobiecki, 2014). Medicines prescribed in TAM are typically classified by colour and the sequence they are given in: *imithi emnyama* refers to black medicines given at night; *imithi ebomvu* are red medicines given at dawn or dusk (e.g., *insizi* or powdered herbs rubbed into incisions); *imithi emhlophe* are white medicines given in the day (Washington, 2010; Sobiecki, 2014). Medicines used in WBM are categorised based on their function (for non-steroidal anti-inflammatory drugs) and can be referred to according to the chemical structure (acetylsalicylic acid), by a generic name (aspirin) or the mechanism of action of the drug (anti-inflammatory) (Ashforth, 2005). In WBM, regulatory authorities (e.g. South African Health Products Regulatory Authority (SAHPRA)) are responsible for regulating health products and medicines to ensure they are safe and effective (Ashforth, 2005). The Medicines and Medical Devices Regulatory Authority Act (Act no. 132 of 1998) in SA legislates the regulation of biomedicine and traditional ('complementary') medicines by SAHPRA. The bureaucratic regulation of traditional medicine has not been successful as traditional healers practice medicine under spiritual authority and not authority from the state (Ashforth, 2005). Generally, western academic critiques of traditional medicines relate to the issues of toxicity, and limited scientific evidence of their efficacy (Bruce, 2002). While an argument can be made that the side effects and contraindications of pharmaceutical medicines are understood and tested, the existence of contraindications and lack of consideration when referring to traditional medicines speaks to the academic bias with which medicines are viewed (Washington, 2010). As Sobiecki (2014) notes, this misconception assumes that pharmaceuticals used in biomedicine are well-tested and approved by regulatory bodies, which is not always the case. Traditional healers prescribe treatments that correlate with reducing symptoms in their patients, leading to the suggestion that TAM is evidence-based (Conco, 1972; Sobiecki, 2014).

Since the beginning of the late 19th century, indigenous medicinal practices in South Africa have been subjected to extensive changes. In 1974, The South African Medical and Dental Council made their rejection of indigenous healers official in the Health Act, which forbade non-registered healers to practice or perform any act pertaining to the medical profession (Edwards, 2010). Registered healers were also forbidden to work in collaboration with non-registered healers (Edwards, 2010). The South African Medical Journal (1976), which is the official organ of the Medical Association of South Africa, a professional and non-statutory organisation, opposed the rejection of healers- its suggestion was that medical professionals attempt to understand the healers' system of operation and accept healers in certain fields while helping them to recognise those illnesses they are unable to cure (Regional Committee for Africa (WHO), 2013). To judge traditional healing knowledge and practices using Western biomedicine's values, philosophies, accountability standards and efficiency measures as a barometer is at odds with local realities (Craffert, 1997).

While some have suggested a two-way model where referral to WBM physicians for curative treatment is paired with indigenous TAM healers for cultural explanation of causation and treatment – this is a form of hegemony over the autonomy of TAM (Pemunta & Tabenyang, 2020a). This attempt to restrict TAM to the confines of WBM theory and practice negates the importance of the indigenous knowledge, heritage, culture and spiritualism that shapes TAM (Washington, 2010; Pemunta & Tabenyang, 2020a). It has been argued that the widespread use of TAM, and its combination with WBM in SA, implies the potential for both these systems to be integrated into the healthcare system (Pemunta & Tabenyang, 2020a). As SA is home to many diverse communities comprising different cultures, languages, religions and belief systems, integrating WBM and TAM within a single healthcare system is contentious given the political, social and economic climate in the country.

1.7.2 Diagnosis and treatment of MJD in the biomedical system

MJD is localised to geographic catchment area of uMkhanyakude Health District. The five district hospitals in uMkhanyakude (Bethesda, Hlabisa, Manguzi, Mosvold and Mseleni) were all originally missionary hospitals until their inclusion in the National Health Department in 1980 (Umkhanyakude Health District: 2021). The Mseleni Hospital has been the primary facility treating MJD for several decades (KwaZulu-Natal Department of Health, 2021). This is likely due to the localisation of sufferers to areas adjacent to the hospital (Lockitch, 1974; Mann & Fredlund, 1988), the involvement of the hospital staff in research and the establishment of the orthopaedic surgery programme (Du Toit, 1979; Viljoen *et al.*, 1993; Fredlund, 2010). The Hospital generally employs 5-8 doctors, including internship and community service doctors and 2-3 physiotherapists, occupational therapists and psychologists. There are thirty-six mobile and nine fixed clinics that fall under the Mseleni Hospital: Gateway, Ezimpondweni, Mabibi, Manaba, Mbazwana, Mduku, Thsongwe, Oqondweni and Mnqobokazi (KwaZulu-Natal Department of Health, 2021). The clinics are managed by senior nursing staff employed at the Mseleni Hospital. Doctors visit the clinics once a week, while the therapists, dentist and social workers visit each clinic once every 2 weeks.

If a patient cannot be treated at the clinic or requires more tests, they will be referred to a Medical Officer at the Outpatients department (OPD) of the Mseleni Hospital. The OPD serves as a doctor's waiting room and a 24-hour emergency department (Fredlund, 2010). Patients with MJD are generally referred from OPD to the radiography department for an X-ray, which is interpreted by the referring doctor. A significant proportion of the radiography at the Hospital is related to TB and MJD (Fredlund, 2010). The Mseleni Hospital reportedly conducts two joint replacements a week due to staff shortages, cost limitations and space shortages (Fredlund, 2003 and 2010). There are 184 beds at the hospital divided between 6 wards comprising labour, female surgical, male, female medical and isolation wards used for TB (Fredlund, 2010) and recently Coronavirus disease of 2019 (COVID-19).

In the absence of discrete criteria, MJD is identified by excluding rheumatoid arthritis, gout, reactive arthritis, spondylarthritis and avascular necrosis as possible causes of joint pain (Agarwal *et al.*, 1997; Fredlund, 2003). To reach a diagnosis, physicians examine physical symptoms, take a patient and family medical history and perform blood tests and like X-rays (Lockitch, 1974; Waller, 1998; Fredlund, 2003). Histories given by patients tend to be similar with the first symptoms including pain in larger joints of the lower limb – the hip, knees and ankle joints (Lockitch, 1974). Regardless of onset age, diagnoses are usually made at advanced-stages of the disease when joint degeneration and pain result in dependence on sticks, walking frames and wheelchairs for mobility (Fellingham *et al.*, 1973). This is because the first symptoms of the disease include crepitus and painful, stiff joint movements, which are unlikely to be cause for concern in a region where physical labour is commonplace (Agarwal *et al.*, 1997). Findings by Lockitch (1974) suggest people with MJD experience pain in larger joints of the lower limb – the hip, knees and ankle joints several years prior to diagnosis. In rural areas in South Africa, the average distance travelled to reach a clinic or hospital is 13km, thus, many sufferers do not visit the hospital in the early stages of MJD (Mann & Fredlund, 1988; Waller, 1998). The mean duration of symptoms prior to MJD diagnosis is estimated to be 17 years and, not surprisingly, 89% of newly diagnosed patients are severely crippled with advanced joint degeneration (Waller, 1998). These statistics suggest that early diagnoses may provide patients with more treatment options and improve the prognosis of MJD (Waller, 1998).

Physicians manage symptoms of MJD during the initial stages as they would an OA – pain reduction and maintaining joint mobility (Fredlund, 2003). Therapeutic interventions at the Mseleni Hospital are designed to maintain the range of movement and improve joint function (Fredlund, 2003). Lifestyle interventions are also recommended to prevent additional strain to weightbearing joints. A combination of NSAIDs (aspirin, ibuprofen, indocid, diclofenac, naproxen and paracetamol and tramadol) are prescribed to alleviate joint pain and stiffness (Fredlund, 2003). NSAIDs are widely used to treat OAs as they are affordable and offer effective pain relief with limited contraindications. However, NSAIDs are not a long-term solution to alleviate symptoms of MJD as acute kidney injury, chronic kidney disease and cardiovascular disease are common in chronic users of NSAIDs (Lipworth *et al.*, 2016).

Surgical interventions, like total hip and knee joint arthroplasties are costly but effective options for pain reduction and improved mobility (Fredlund, 2003). Patients, however, rarely experience full functional recovery and targeted prevention of the underlying aetiology of MJD may be more effective in reducing the burden of disease (Fredlund, 2003). Surgical intervention is an unfeasible long-term treatment strategy for MJD as the Mseleni Hospital lacks the capacity and financing to regularly conduct more than 2 total joint replacements per week (Mann & Fredlund, 1988; Fredlund, 2003; Fredlund, 2010). Understanding the pathophysiology of MJD is essential to develop drugs that can treat both pain and joint degeneration with few immediate or long-term effects.

1.8 Theoretical frameworks

Philosophical assumptions and paradigms are often unmentioned in scientific research, despite the fact that these impact the research question, actions of the researcher and outcomes of the research (Wahyuni, 2012). There are several philosophical paradigms used to organize research (for example, postpositivism, constructivism and pragmatism) and these encompass the following common elements: axiology, ontology, epistemology and methodology (Creswell *et al.*, 2011; Kaushik & Walsh, 2019). Axiology refers to the role of values, ethics and the individuals stance in shaping the overall research narrative (Wahyuni, 2012; Kaushik & Walsh, 2019). Ontology is the “study of being” (Crotty, 1998: p.10) and is concerned with the nature and existence of reality (Wahyuni, 2012). Epistemology is concerned with knowledge, specifically how knowledge is created generated, acquired and communicated (Wahyuni, 2012) and methodology is the strategy or plan underlying selection of specific methods to collect and analyse data (Creswell *et al.*, 2011; Wahyuni, 2012). Understanding how axiology, ontology and epistemological manifest themselves in the methodology and methods of a study is critical to the comprehension and application of research findings. Postpositivism as a paradigm is associated with quantitative methods and highly formal rhetoric, with a focus on precision, generalizability, reliability, and replicability (Kaushik & Walsh, 2019). Ontologically, postpositivism is predicated on the view that reality is objective and exists independently of human values, thoughts or beliefs (Wahyuni, 2012). While research is seen as value laden, influenced by worldviews, culture and upbringing (axiology)

The epistemological perspective maintains that phenomena are observable and can be described within a particular context. Notably, this advocates the use of either quantitative or qualitative methodologies to. Within postpositivism, researchers view inquiry as a series of logically related steps and make claims of knowledge based on objectivity, standardization, deductive reasoning, and control within the research process (Creswell, 2009; Kaushik & Walsh, 2019).

This differs greatly from constructivism which is associated with qualitative methods and informal rhetoric (Kaushik & Walsh, 2019). Constructivism acknowledges the researchers role in shaping the research narrative, and as the researcher is part of what is being research – the researchers voice and narrative are inseparable from the outcome which will thus be subjective. Within this reality is constructed and the researcher must rely on participants’ views and attempt to develop subjective meanings of phenomena under study (Creswell *et al.*, 2011). Constructivist research is shaped from the bottom up, starting from individual perspectives to broad patterns and ultimately to broad understandings of concepts and themes (Kaushik & Walsh, 2019).

While postpositivist and constructivist research approaches are anchored on opposite sides of a paradigm continuum, pragmatism claims to bridge this gap (Kaushik & Walsh, 2019). Pragmatism is predicated on the existence of both objective and subjective elements of reality – informed by experiences, actions and inquiry (Dewey & Hahn, 1985; Creswell *et al.*, 2011). This paradigm embraces the use of the scientific method and structuralist orientation as well as the naturalistic methods and more flexible orientations of newer approaches (Creswell *et al.*, 2011). As such pragmatism is frequently used in mixed- and multi-methods research where the focus is the consequences of the research and the research questions rather than the philosophical approach (Tashakkori *et al.*, 1998; Weiner, 2007; Creswell, 2009). Pragmatism sidesteps contentious debates on concepts such as truth and realism and instead accepts the existence of single and multiple realities, which are open to both empirical and theoretical forms of enquiry (Creswell *et al.*, 2011). A mixed methods study using quantitative and qualitative methods can be used to explore different facets of the same problem as they are united by the same goal – understanding phenomena systematically and coherently (Tashakkori *et al.*, 1998; Bryman, 2007).

Within pragmatism, quantitative data analyses (descriptive statistics, regression analyses and factor analyses) are methodologically conceptualised as exploratory, while qualitative data analyses (grounded theory, thematic analysis, phenomenology) are explanatory and confirmatory (Onwuegbuzie & Leech, 2005). Moreover, Onwuegbuzie & Leech (2005) highlighted several pragmatic approaches used to combine quantitative and qualitative data in mixed methods research: (1) triangulation (seeking convergence and corroboration of results from different methods studying the same phenomenon); (2) complementarity (seeking elaboration, enhancement, illustration and clarification of results between methods); (3) development (using the results from one method to help inform the other method); (4) initiation (discovering paradoxes and contradictions that require re-framing the research question) and (5) expansion (expanding the range of enquiry by using different methods for different inquiry components). By conducting mixed methods research based in pragmatism, empirical and theoretical precision can be combined to facilitate micro- and macro- levels of discourse on a single research problem.

The biocultural approach is particularly useful in understanding risk factors as it provides a framework for modelling the dynamic interactions among biological/phenotypic, psychological and sociocultural factors in response to the environment (McElroy, 1990). In this framework, human biological variability is viewed as a function of responsiveness to the environment with a specific focus on sociocultural factors (Khongsdier, 2007). When the stressors an individual experiences exceed biological or cultural buffering systems, the negative effects on the body are known to include impaired immunity (Mushrif-Tripathy, 2014), reduced growth (Himmelgreen *et al.*, 2014) and predisposition to

chronic and degenerative diseases (Lai & Lovell, 1992). Thus, the biocultural framework acknowledges that diseases are the result of biological plasticity and responsiveness to environments that both mediate and produce each other (Zuckerman & Martin, 2016). In this way, social, cultural and environmental factors are not considered a backdrop for disease determinants but are considered causes in their own right (Krieger, 2000; Leatherman & Goodman, 2011).

1.9 Aims and objectives

The above review has emphasised the paucity of knowledge pertaining to the aetiology, differential diagnosis and treatment of MJD. Given the unique localisation and pattern of MJD, a complex, multifactorial aetiology comprising several environmental, social, cultural and perhaps epigenetic (and genetic factors) seems likely. An updated measurement of the distribution of MJD is central to identifying risk factors so that this disease can be better managed. Furthermore, insight into how MJD is understood and experienced by affected individuals and healthcare providers is needed to formulate care strategies to mitigate the burden of disease. A mixed methods study was conducted to assess risk factors, explanatory models and treatment-seeking behaviours linked to MJD within a biocultural, pragmatist framework.

Aims

1. Identify biological, spatial and sociocultural risk factors associated with MJD.
2. Examine explanatory models of MJD and treatment seeking behaviours held by MJD patients and WBM healthcare providers.

Objectives

1. Examine the onset, pathology and differential diagnosis of MJD using medical records and surveys of MJD patients at the Mseleni Hospital.
2. Identify demographic and environmental risk factors of MJD using a cross-sectional medical record review at the Mseleni Hospital and surveys of MJD patients.
3. Identify temporal changes in the demographic and geographic distribution of MJD from a meta-analysis of the literature.
4. Assess environmental and socio-economic risk factors using a socio-ecological analysis of national census data and community surveys.

5. Identify explanatory models of MJD by assessing explanations of the onset, aetiology, pathophysiology, course of disease and treatments of MJD from interviews with MJD-affected individuals, nurses and doctors at the Mseleni Hospital.
6. Assess the relationship between explanatory models and treatment-seeking behaviours from interviews with MJD-affected individuals, nurses and doctors at the Mseleni Hospital.

Chapter 2: Materials and Methods

A mixed methods study was designed to assess risk factors, explanatory models and treatment-seeking behaviours associated with MJD. The methods used to collect and analyse data from medical records, semi-structured surveys, in-depth interviews, census publications and the epidemiological literature (meta-analysis) are described below.

2.1 Methodology

A biocultural mixed methods study grounded in the pragmatist framework was used. Quantitative data were collected from medical records at the Mseleni Hospital, socio-ecological surveys of MJD-affected and unaffected individuals, SA national census publications and the epidemiological literature pertaining to MJD. Qualitative data were collected from in-depth interviews of MJD patients, nurses and doctors at the Mseleni Hospital. These methods were selected to compare biomedical-perspectives, and patient-perspectives of MJD. Quantitative data were collected to assess risk factors, pathology, onset and treatment of MJD, while qualitative data were used to develop themes relevant to explanatory models and treatment-seeking behaviours. This cross-sectional study was designed to measure prevalence and risk factors. Causal pathways and risk factors assessed in this study are depicted in

Figure 2.1. Methods were mixed through triangulation, convergence and corroboration of results from different quantitative and qualitative findings pertaining to the same phenomena.

2.2 Ethical considerations

This study was compliant with ethical guidelines stipulated in the Declaration of Helsinki (2008) and the Department of Health: Ethics in Health Research: Principles structures and Processes (2004). Ethical approvals were granted by the University of Cape Town Human Research Ethics Committee (HREC: 079/2019), the Mseleni hospital, the uMkhanyakude district health authority and the KwaZulu-Natal (KZN) Provincial Department of Health (Figures B1-4) (KZ_201902_002). All individualising information was anonymised to ensure privacy and protection of participant identifies.

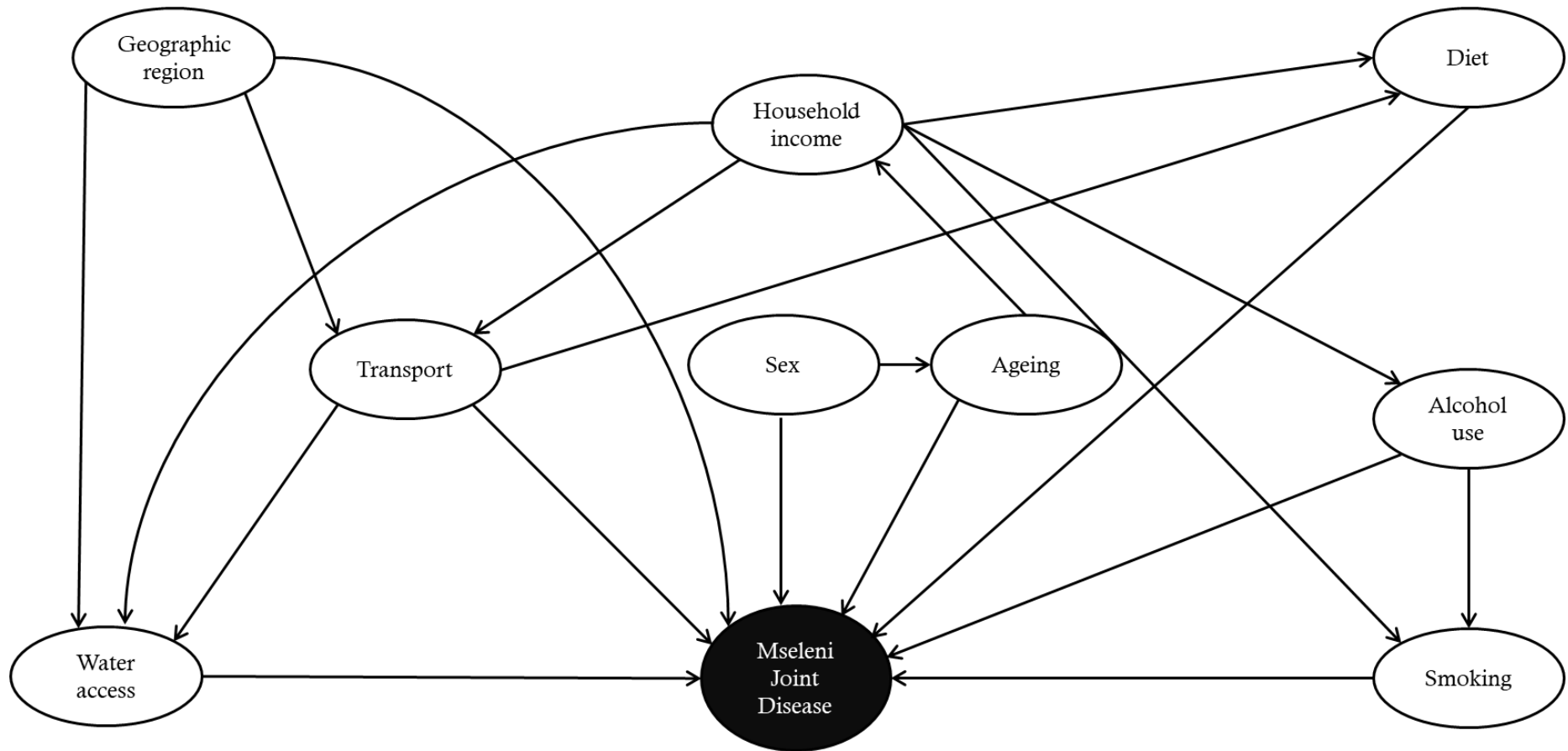


Figure 2.1. Directed acyclic graph (DAG) showing causal pathways assessed in this study. Nodes represent variables and arrows represent causal associations. The white nodes represent possible causes or confounding factors, while the dark-coloured node represents Mseleni Joint Disease.

2.3 Data collection

2.3.1 Medical records

A medical record review of patients visiting the OPD at the Mseleni hospital in May 2019 was conducted in July 2019 to assess the point prevalence, demographic risk factors and geographic clustering of MJD. Prior to sampling, a formula developed by Daniel (1999) was used to calculate the sample size required to assess the point prevalence of MJD with precision:

$$n = \frac{Z^2 \cdot P(1 - P)}{d^2}$$

Here n is the sample size, Z is the statistic corresponding to level of confidence, P is the expected prevalence obtained from previous studies or a pilot study, and d is precision (corresponding to effect size). To assess MJD prevalence without oversampling, sample size was enumerated using confidence levels of 95%, a last known prevalence of 5.1% (Yach & Botha, 1985) and a precision of 2%. Accordingly, a minimum sample of 465 individuals was enumerated to estimate point prevalence. This study was designed to identify and assess MJD in people seeking medical assistance at the Mseleni hospital and could undercount asymptomatic individuals, patients treating their symptoms with over-the-counter medication and severely disabled or impoverished patients with poor access to transport and healthcare.

The OPD was selected as a sampling frame because the Mseleni Hospital lacks a centralised administrative system or electronic medical records, and therefore, obtaining a representative sample of all hospital patients was not feasible in the study time frame. While reviewing records from several of the 45 clinics managed by the Mseleni hospital was considered, the lack of consistent record keeping may have compromised reliability. The OPD was selected for this medical record review because patients presenting at regional clinics with joint pain and stiffness are generally referred to this department for diagnosis, clinical assessments, and treatment. The OPD serves three primary functions: a reception unit for patients who require medical attention, but not hospital admission; an emergency care facility; a clerical service for hospital admissions, facility/hospital transfers, day-clinic visits and storage of patient folders for appointments with therapists, radiologists and physicians. Sampling from the OPD may therefore provide the most reliable estimate of the burden of MJD on the Mseleni hospital. The lack of temporality in assessing if the putative causes preceded the development of MJD and limited sampling frame will remain limitations in the assessment and discussion of risk factors.

Medical records were requested for the population-at-risk defined *a priori* as: SABP people of Zulu language, older than 6 years, from the affected uMkhanyakude municipal district or adjacent municipalities. For cross-validation, two investigators recorded gender, date-of-birth, district of residence and reason for the OPD visit from each medical record. A detailed clinical history was captured for each MJD patient with a focus on the diagnostic assessments, symptoms, pathology, disease duration, treatment, and outcomes over the patient's follow-up period.

2.3.2 Survey instruments

Four semi-structured surveys comprising open-and closed-response questions were designed to collect quantitative and qualitative data from uMkhanyakude residents (unaffected and MJD positive individuals) and healthcare providers (nurses and doctors). The procedures used to develop and optimise surveys are described below, and results from the survey development phase are reported in Chapter 3.

2.3.2.1 Survey design

Textual analyses of interviews from two unpublished studies on MJD undertaken in June 2013 and July 2017 were used to the design semi-structured surveys. Interviews took place at the Mseleni Hospital on the 19th of June 2013 and the 24th of July 2017 during sampling for two DNA sequencing studies. Ethical approvals for these studies were obtained from the University of New Brunswick Research Ethics Board (REB 2013-047), University of Cape Town Human Ethics Committee (HREC 822/2015), Yale University Human Ethics Committee (REB 120100962), the Mseleni Hospital, uMkhanyakude Health District Office and the Province of KwaZulu-Natal Department of Health (HRKM 052/13) (Figure B5-6).

Interviews were conducted with 12 MJD patients and a doctor (the Medical Manager at the Mseleni Hospital) in 2013, and 19 MJD patients in 2017. These studies purposively recruited adults (older than 18 years of age) who were receiving care for MJD at the Mseleni Hospital and had been diagnosed with MJD at least five years prior to the commencement of these studies. With the help of two translators, informed consent was obtained from all patients in Zulu, and thereafter, interviews conducted in Zulu were translated and transcribed into English. Interviews took place at the Mseleni Hospital, and all patients were provided with transport and refreshments as remuneration for participation.

The first set of interviews (2013) included only broad discussion points with a focus on the clinical history of MJD (duration of disease, pathology, and treatment). The second set of interviews (2017) were semi-structured, with open and closed-response questions focussing on clinical history, geographic localisation, family history of MJD and lifestyle practices (subsistence activities, water sources and dietary practices). For both sets of interviews, researchers solicited information when

patients provided vague or unclear answers. Findings from these interviews were used to design, semi-structured surveys to collect quantitative and qualitative data. Semi-structured surveys contain a combination of closed-and open-ended questions (Kroeger, 1983; Moolenburgh *et al.*, 1986). Closed-ended questions are well-suited for quantitative analyses as they require a participant to select an option from a set of pre-defined responses (*e.g.*, Do you have this condition?) (Ferketich *et al.*, 1993; Brewster *et al.*, 2019). While open-ended questions are adaptable for quantitative and qualitative studies, they are best suited for studying phenomena that require the respondent to elaborate on their responses (*e.g.*, What treatment are you undergoing for this condition?). Where possible, the categories and questions included in surveys designed for this study were based on clinical and social surveys of MJD developed by Lubbe (1973); Lockitch (1974); Mann & Fredlund (1988).

Four surveys were designed for this study:

1. A socio-ecological survey to assess the socio-economic conditions, cultural practices and lifeways of MJD-affected and unaffected individuals (Figure C1).
2. An MJD survey to assess experiences of the onset, symptoms, course of disease and treatment disease in MJD patients (Figure C2).
3. A survey for nurses at the Mseleni Hospital to assess their experiences and perceptions of MJD (Figure C3).
4. A survey for doctors at the Mseleni Hospital to assess their experiences and perceptions of MJD (Figure C4).

2.3.2.2 Survey administration

The first phase of surveying took place in waiting rooms at the OPD, Gateway clinic and Therapy unit at the Mseleni hospital between the 7th and 22nd of June 2019. A translator was trained to facilitate with obtaining informed consent and administering surveys in Zulu. Consent forms and information sheets were translated from English into Zulu and patients were given the option of reading information (in either language) or having the information explained to them (Figures C1-2). Participants were informed of their right to withdraw from the study at any point without prejudice or victimisation. A post-survey debrief was conducted with the translator for the first 10 surveys to identify and address potential problems with communication and patient responses. An outcome of this debrief was to exclude repeated questions that were placed throughout the survey to assess respondent consistency. This decision was taken as participants perceived repeated questions to indicate a lack of trust in the original answers, resulting in visible frustration and discomfort.

According to results from the power analyses, a minimum sample of 30 individuals per group (MJD-affected and-unaffected uMkhanyakude community members) was required to assess risk factors in surveys (Moolenburgh *et al.*, 1986; Brown *et al.*, 2018; Mchunu *et al.*, 2019). The socio-ecological

survey (Figure C1) was administered to 100 uMkhanyakude community members, defined *a priori* to include only SABP adults (older than 18 years of age), who were born in uMkhanyakude or who were residents in the area for at least 15 years (Appendix D1). The disease-specific survey (Figure C2) was administered to 40 individuals with self-reported MJD. As some participants were visiting the hospital for joint pain, self-reported MJD diagnoses were recorded for all participants as “positive” (patients with a formal diagnosis), “negative” (patients with no joint pain, and no formal MJD diagnosis or potential diagnosis) or “unknown” (patients seeking care for joint pain, with no formal MJD diagnosis or uncertain of their diagnosis). After surveys were completed, self-reported MJD diagnoses were confirmed from medical records. Participant responses were translated and transcribed during surveys and captured electronically in Microsoft Excel® when the study was completed.

2.3.3 Interviews

In-depth interviews were conducted with 6 MJD patients, 9 nurses and 7 doctors working at the Mseleni Hospital. Surveys in Appendix C were used to guide interviews. The sample of MJD patients was purposively selected to include those with widespread joint pathology, and a history of treatment and surgery at Mseleni Hospital. Healthcare providers included doctors (specifically medical officers) and nurses (professional nurses) with variable experience at the Mseleni Hospital. All interviews took place at the participants location of choice (at home/work).

Informed consent was obtained for all participants and interviews were conducted in the participants language of choice (Zulu for MJD patients and English for healthcare providers) (Figures C2-4). All Interviews were recorded using an Olympus® (VN-541PC) digital voice recorder, translated into English (where necessary) and transcribed verbatim into Microsoft Word® by three individuals. Transcripts were cross-checked for accuracy, and any differences in translations were discussed with the Principal Investigator of this study until a consensus was reached.

2.3.4 Meta-analysis

A meta-analysis was conducted to assess the prevalence of MJD and evaluate age, sex and geographic localisation as risk factors. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher *et al.*, 2010) were used to design the literature search strategy, assess the quality of research and analyse data. The literature search conducted on the 30th of October 2020 involved searching electronic PubMed, Medline, EMBASE databases using the following descriptors: “Mseleni joint disease” OR “Mseleni” OR “MJD” [All fields]. Reference lists from retrieved articles were manually searched to identify literature that was not identified in the original search.

Published studies were only included in the meta-analysis if they provided prevalence figures or rates of MJD in men, women, and/or different age groups and/or geographic regions. Studies were evaluated for quality and strength of evidence using a reliability assessment scoring system used by Jones *et al.* (1995), Srikanth *et al.* (2005) and Usenbo *et al.* (2015) (Table 2.1). Articles that attained reliability scores greater than 6 (with a maximum possible score of 12) were included in the meta-analysis. Data were extracted by the author and validated by the principal investigators of this study. Where prevalence rates were reported, numbers of people with MJD were calculated based on the sample at risk. When sex-or age-stratified data were available, numbers of affected men and women were extracted for analyses.

Table 2.1 Reliability scoring system used to assess strength of evidence of studies included in the meta-analysis.

| Criteria | Scores | | |
|--|---------------|--------------------|-----------------|
| | 0 | 1 | 2 |
| Sampling procedures [†] | Not stated | Non-random | Random |
| Representative sample [◊] | Not stated | No | Population |
| Sample size calculations [◊] | No | | Yes |
| Sample response rates [†] | Not stated | < 50% | ≥50% |
| Case definitions [†] | Self-reported | Clinical diagnoses | X-Ray diagnoses |
| Standardised radiographic diagnoses [†] | No | | Yes |
| Reported diagnostic reliability [†] | No | | Yes |

Standards for reliability scoring: [†] Jones et al. (1995) and Srikanth et al. (2005); [◊] Usenbo et al. (2015).

2.3.5 Census publications

Socio-ecological conditions in the Umhlabuyalingana municipal wards were assessed using data from the South African National Census in 1996, 2001 and 2011. A fourth census planned for 2019/2020 was postponed too October 2021 due to COVID-19. Demographic, socio-economic and environmental data were extracted from SuperWeb2® for local municipal wards 1-17 in Umhlabuyalingana. To identify macro-indicators of socio-economic development and environmental change in regions at risk of MJD, percentages (within districts) were extracted and mapped for municipal districts in uMkhanyakude. The following data fields were used to collect data: population size (regional and average per household); employment rate (employment types, average household income, number of disability grants per household); infrastructure development (housing types and number of residents per

household); resource availability (access to water, sanitation, electricity, education, transport and healthcare); lifeways (marriage practices; religion; language spoken and cooking methods).

2.4 Data analysis

All data were entered into Microsoft Excel® for quantitative analysis and Microsoft Word® for qualitative analyses. Unless otherwise stated, data were analysed and graphed in R Studio® or NVivo®. An alpha value of $\alpha = 0.05$ was selected as the level of significance. Bonferroni adjusted alpha values were computed to correct for the effect of multiple comparisons and possible Type I errors (Abdi, 2007). The formula below was used to calculate adjustments:

$$\alpha_{Bonferroni} = \frac{\alpha}{m'}$$

Here α is the alpha value established *a priori* as 0.05, and m' is the number of tests/comparisons.

2.4.1 Quantitative analysis

All continuous data were assessed for normality graphically using box-and-whisker plots and statistically using Shapiro-Wilk tests (Shapiro & Wilk, 1965). Thereafter, the relevant descriptive statistics were computed for parametric (mean and standard deviation) and nonparametric data (median and inter-quartile range).

2.4.1.1 Demographic and spatial distribution

A period prevalence of MJD was calculated from medical records using the following formula: (Bagley & Altman, 2016)

$$\text{Period prevalence} = \frac{\text{No. of people with a disease in a defined population at one point in time}}{\text{Total no. of people in the defined population at the same point in time}} \times 100$$

Demographic risk factors (age and gender) were assessed using X^2 tests of association and logistic regression analyses. A logistic regression analysis was conducted to assess the association between gender, age and MJD. Standard age intervals used in arthritis research (Brennan-Olsen *et al.*, 2017) were used in analyses of medical record and survey data (31-40 years; 41-50 years; 51-60 years; 61-70 years; 71-79 years; 80+ years). These findings were compared to prevalence figures from each study included in the meta-analysis. To facilitate the comparison of papers identified in the meta-analysis, age categories reported by each study were utilised and combined where necessary to allow comparison (0-29 years, 30-49 years, 50-69 years and 70+ years) (Fellingham *et al.*, 1973; Yach & Botha, 1985). Forest plots of the odds ratios (OR) and 95% confidence intervals (CI) of MJD were graphed according to

gender and age to assess the temporal distribution of MJD using the meta-analysis and medical record review data. Due to limited data, a test for heterogeneity could not be used in the meta-analysis, and as a result a combined odds ratio estimate was not calculated.

The spatial clustering of MJD was assessed using patient-reported residential addresses mapped according to local wards and district municipalities. A map of municipal and district demarcations used in the National Census of South Africa in 2011 was used to map geospatial localisation of MJD in the affected region. The map of districts in the MJD-affected area map has remained largely consistent since 1996, with one change - the subdivision of ward 9 into wards 9 and 18. Determining where the demarcation changes occurred was not feasible and these wards were assessed collectively as Ward 9. Prevalence frequencies were graphed for each local district with more than five patients. The decision was taken to exclude districts with fewer than five patients visiting the OPD during the sampling period, to prevent the small sample sizes from biasing strength of association in these regions.

Global positioning system (GPS) co-ordinates obtained for each patient's home addresses, (or nearest clinic in many cases where addresses were not reported) were plotted relative to concrete/tarred roads, water sources (lakes, dams and rivers), water distribution pipelines and the Mseleni Hospital.

2.4.1.2 Pattern of pathology, onset and treatment

Data from medical record reviews and MJD patient surveys were used to assess the pathology, onset and treatment of MJD. Associations between demographic variables (sex and age) and the mode of onset, the onset age (and diagnosis age) and joints affected at onset were assessed using X^2 tests of association. Using clinical data and survey responses, the joints affected at onset were compared to the joints affected at the time of sampling for MJD patients who had been receiving treatment for MJD for 0-5 years, 5-10 years and more than 10 years. The symptoms (joint pain, swelling, limited range of movement and radiating limb pain) and co-morbidities were assessed for their association with MJD using X^2 tests.

2.4.1.2 Socio-ecological risk factors

Socio-economic factors and lifeways assessed in surveys and census publications were tested for their association with MJD using X^2 tests of association and where possible, logistic regression analyses. Data from census publications and patient-surveys were mapped to detect macro-level associations between MJD, socio-economic indicators (transport access, tapped water access, and household income) and lifeways in different districts.

2.4.2 Qualitative analysis

Explanatory models of MJD and treatment-seeking behaviours were assessed using a thematic analysis of open-ended responses from surveys and interviews of MJD patients, doctors and nurses at the Mseleni Hospital. These data were divided into two groups according to sampling period (2019 and 2020) and responses from patients, doctors and nurses were assessed separately employing within-case analysis (Boyatzis, 1998). The steps in coding, sorting and merging, and identifying themes were applied systematically to maximise the validity and reliability of each subsequent step. The themes emerging in analyses of interviews were refined through comparison with survey responses.

Interview transcripts were read by the author and Principal Investigator prior to analysis. The first step in analysis was open coding, which involved summarising each line of the interview transcripts to identify trends, categories and patterns (Boyatzis, 1998). This stage was inductive and did not use any predetermined codes or a 'coding dictionary', instead codes were created as new concepts emerged (Thornberg & Charmaz, 2014). The second step in this analysis was axial coding, which involved combining similar codes and then developing categories or groups of common codes (Braun & Clarke, 2006). Where relevant, codes were grouped according to Kleinman's Explanatory model framework (1980). This led to the development of themes which were defined as abstract entities providing meaning and identity to recurrent responses and experiences (Braun & Clarke, 2006). Themes were identified by bringing together components or fragments of ideas and experiences, which often appear inconsequential when viewed alone but provide information in relation to the overall research question (Braun & Clarke, 2006). Selective coding was the final step in analysis and involved making logical connections between the core categories and themes to make sense of observed practices and experiences (Wahyuni, 2012).

Employing an inductive approach ensured that the emergent themes were strongly linked to the data and not necessarily the questions that guided interviews. In this sense, this thematic analysis was data-driven (Braun & Clarke, 2014) and the themes reflected individual perspectives of the participants'. The validity of these findings was enhanced by employing different types of triangulation: methodological triangulation (the data collected in surveys in 2019 and individual interviews were compared and contrasted for different participant groups) and investigator triangulation (multiple members of the research team contributed to data analysis and provided feedback on coding and theme identification) (Patton, 2002; Wahyuni, 2012).

Sections of original transcripts considered illustrative of the emergent themes are included as quotations in the results. To avoid treating participants as research 'specimens', no participant identification codes are reported and unless relevant to interpretation, age and gender were excluded from quotations.

Chapter 3: Results

Findings pertaining to biological, geographic, sociocultural factors and explanatory models of MJD are reported in this section. The outcomes from analyses of interviews conducted by the Associate Professor Gibbon in June 2013 and July 2017 are presented with emphasis on the main results that shaped the survey design detailed in Chapter 2. Thereafter, the quantitative findings from analyses of medical records, semi-structured surveys and census publications are reported. Finally, the main themes pertaining to the perceptions of causality, experiences of healthcare and attitudes towards treatment in MJD patients and healthcare providers are described.

3.1 Survey development

The interviews conducted in 2013 measured age-of-onset (using date of onset and explanation of symptoms), location of pathology and treatment, while the 2017 interviews assessed the variables investigated in 2013 with the addition of family history (prevalence of MJD in families) environmental exposures (geographic region of residence and water sources) and lifestyle factors (diet, drinking habits and activity levels). A total of 31 patients were interviewed (12 sampled in 2013 and 19 in 2017) (Figure 3.1A) and the Medical Manager at the Mseleni Hospital (2013). The sample was skewed in its representation of women and patients older than 50 years (Figure 3.1A). Only two patients (sampled in 2017) had brachydactylous dwarfism and there were no differences in responses between these individuals and MJD-affected patients of regular stature.

3.1.1 Pathology and onset of MJD

Approximately 97% (30/31) of individuals provided responses about joints affected by MJD during the time of sampling. Patients most frequently reported pain in the ankle, knee then hip joints (Figure 3.1B and Table D1). All respondents reported experiencing pain in the appendicular skeleton (upper and lower limbs), with the hips most frequently affected (90%, 27/30) (Figure 3.1B and Table D1). Pain in the lower back was reported by 30% (9/30) of patients (Figure 3.1B). Approximately 33% (10/30) of patients reported bilateral radiating pain in the hip and thigh regions (Table D1). The pilot interviews contained no temporal data on the incidence of pain in different joints, and this was expanded upon in later surveys.

There was no consensus about events leading to onset of MJD or the age that patients first experienced pain. All patients reported the onset of symptoms at least 10 years prior to the sampling periods. One patient with bilateral joint immobility described the onset of MJD occurring during the sampling year (2013), indicating communication regarding the initiation of symptoms and diagnosis of MJD needed to be improved in subsequent surveys.

Two patients recalled an early onset of pain in childhood, while 8 patients (6/7 in 2013 and 2/17 in 2017) described onset relative to the childbirth. The link between childbirth and MJD onset was notable, one participant recalled onset relative to the birth of a first child, while two others recalled the onset after the birth of their third and fourth children (Figure 3.1C and Table D2). Not all the women with children could link onset of MJD to childbearing.

3.1.2 Risk factors of MJD

Only participants interviewed in 2017 were asked questions pertaining to a family history of MJD, and environmental and lifestyle factors. Approximately 79% (15/19) of participants reported a family history of MJD, and 32% (6/19) of respondents reported at least one affected family member while 47% (9/19) two or more (Figure 3.1D and Table D2). Participants reported a higher prevalence of MJD in female relatives (42%; 8/19) (specifically mothers, sisters and aunts) than male relatives (11%, 2/19) (Appendix D: Table D2).

The spatial localisation of MJD was assessed and inconsistency in how participants relayed geographic residence was noted. Participants either listed their nearest settlement or town (*e.g.* Mseleni or Mlamula) or municipal district (uMkhanyakude). All patients described similar staple diets comprising meat, vegetables, and fruit. All participants noted consuming locally grown ground nuts. When asked about drinking habits, 58% (11/19) of patients had never consumed alcohol, while 37% (7/19) claimed to be past drinkers of traditional Zulu beer. Regarding how they obtained water for household use, 18/19 participants reported that their water source had changed from off-plot water sources (rivers or communal boreholes) to tapped water. As no additional information could be extracted from the vague responses pertaining to changes in water and food sources, survey instruments developed from these data included detailed questions to assess risk factors. To obtain more precise temporal estimates of when changes in socio-ecological conditions occurred the following age categories were used (0-5 years, 5-10 years, 10-15 years and <15 years) (Figure C1).

3.1.3 Treatment of MJD

Approximately 52% (16/31) of patients mentioned using only analgesia for pain management, while 32% (10/31) noted joint arthroplasty in addition to analgesia (Figure 3.1E and Table D2). Approximately 7 participants reported undergoing one or more hip arthroplasties, while 3 patients reported knee replacements. One patient interviewed in 2013 had undergone five surgical procedures since 1989 for revision of prosthetics from total hip arthroplasties.

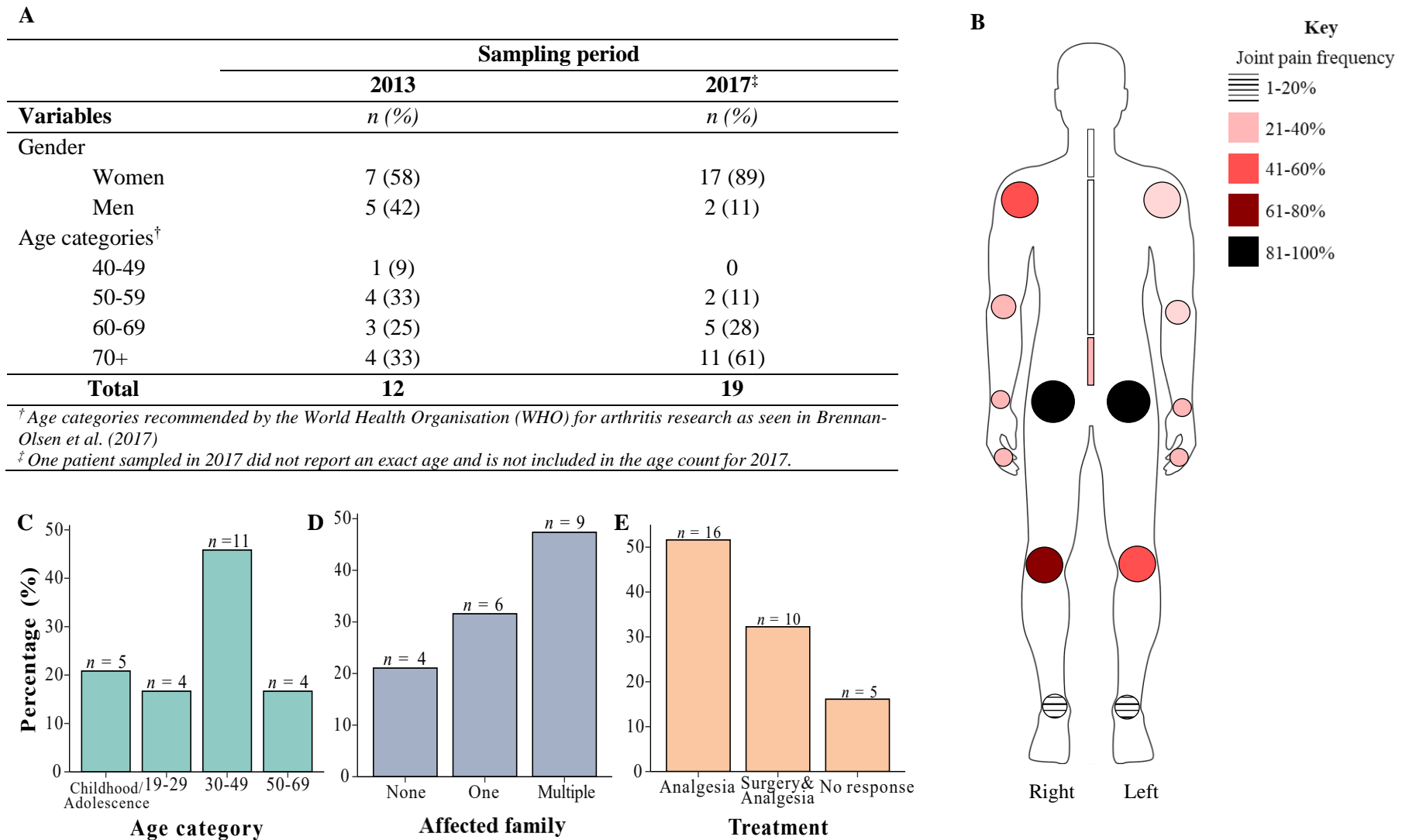


Figure 3.1 Distribution and participant responses from interviews of patients with Mseleni Joint Disease (MJD) conducted by Associate Professor Gibbon in 2013 and 2017. (A) Gender and age distribution of patients with MJD interviewed in 2013 and 2017; (B) heatmap showing frequency of joint pain reported by patients with MJD in 2017. Participant responses in 2017 pertaining to (C) onset age, (D) family history and (E) treatment of MJD.

3.2 Study sample characteristics

Medical records were requested for 1409 patients visiting the OPD at the Mseleni Hospital in May 2019 (Table 3.1). Only 723 individuals satisfied the inclusion criteria, defined *a priori* as SABP older than 6 years-of-age, from the uMkhanyakude or adjacent municipalities. Sample patients visited the OPD for a variety of reasons, the most common were tooth extraction/dentist appointments (10%), trauma/medical emergencies (12%) and joint pain (9%) (Table D3). Only 39% (26/66) of the patients visiting the OPD for joint pain had MJD, and the remaining patients with joint pain were diagnosed with other conditions (such as metastatic cancers, systemic lupus erythematosus or rheumatoid arthritis).

Socio-ecological surveys were conducted with 99 participants (45 MJD-affected and 54 unaffected individuals) at the Mseleni Hospital (Table 3.1). Only 37 participated in MJD-specific surveys. More women (79/99) than men were sampled (20/99) and the median age was 55 years \pm 26 years (Table 3.1). Only 1 patient with MJD was surveyed and sampled in the medical record review, and there was perfect agreement between patient-reported and doctor-recorded information.

The literature search for the meta-analysis yielded 51 records of articles (Table D4). In the first round of screening, 15 articles not MJD were excluded. A further 29 articles were excluded due to lack of research on the distribution or prevalence of MJD. Of the seven studies assessed for reliability and strength of evidence, and only four qualified for inclusion in the meta-analysis (Figure 3.2 B).

Table 3.1 Medical record review, survey and interview sample summary.

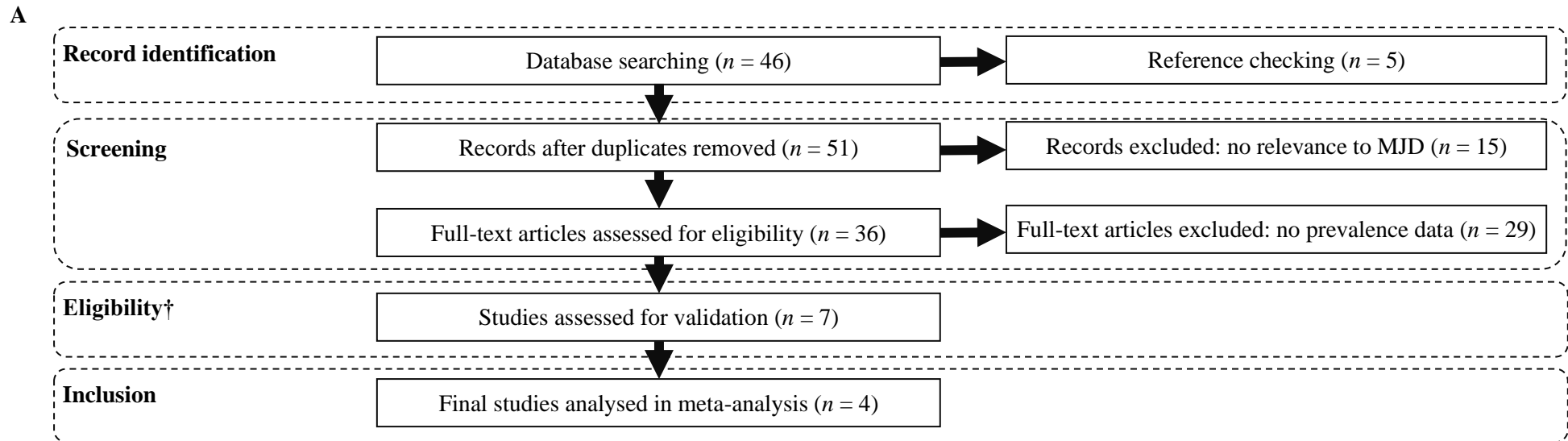
| | Women (n) | Men (n) | Total participants (n) |
|------------------------------------|-----------|---------|------------------------|
| Medical records | | | |
| Total patients [†] | 496 | 297 | 1409 |
| At-risk patients | 446 | 277 | 723 |
| Patients with MJD | 49 | 17 | 66 |
| Case reviews [‡] | 37 | 16 | 53 |
| Surveys | | | |
| Total participants surveyed | 79 | 20 | 99 |
| MJD-positive patients [◊] | 34 | 3 | 37 |
| MJD-unaffected patients | 37 | 17 | 54 |
| Interviews | | | |
| Patients | 4 | 2 | 6 |
| Nurses | 5 | 2 | 7 |
| Doctors | 3 | 6 | 9 |

MJD-Mseleni Joint Disease; n- number of individuals. No gender reported for 616 patients.

[†] *Patients visiting multiple times in May: n=88, thus a total of 1497 visits were registered in May 2020.*

[‡] *Complete and comprehensive diagnostic and treatment information was only available for 53/66 patients.*

[◊] *Approximately 45 MJD patients were surveyed in socio-ecological surveys, but only 37 participated in disease-specific surveys.*



B

| Article reference | Sampling procedures [†] | Representative sample [◇] | Sample size calculation [◇] | Sample response rates [†] | Case definitions [†] | Standardised radiographic diagnoses [†] | Reported diagnostic reliability [†] | Total |
|----------------------------------|----------------------------------|------------------------------------|--------------------------------------|------------------------------------|-------------------------------|--|--|-----------|
| Mann (1984) | 1 | 2 | 0 | 0 | 1 | 0 | 0 | 4 |
| Wittman & Fellingham (1970) | 0 | 1 | 0 | 0 | 2 | 1 | 0 | 4 |
| Fellingham <i>et al.</i> (1973)* | 2 | 2 | 2 | 1 | 1 | 0 | 0 | 8 |
| Lockitch (1974)* | 2 | 2 | 2 | 1 | 2 | 0 | 0 | 9 |
| Lockitch <i>et al.</i> (1973b) | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 4 |
| Yach & Botha (1985)* | 2 | 2 | 2 | 2 | 1 | 0 | 1 | 10 |
| McLaren <i>et al.</i> (1987)* | 2 | 2 | 2 | 1 | 0 | 0 | 0 | 7 |

*Studies included in the meta-analysis scoring reliability scores of ≥ 6 , with scores in bold. Standards for reliability scoring standards: [†]Jones *et al.* (1995) and Srikanth *et al.* (2005); [◇]Usenbo *et al.* (2015).*

Figure 3.2. Selection criteria and reliability scoring used to select literature included in the meta-analysis. (A) The preferred reporting items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines used to select literature assessed in this study ([†]Results from eligibility scoring in B, image adapted from <http://www.prisma-statement.org>). (B) Reliability scoring of research studies and articles assessed for inclusion in the meta-analysis.

In-depth interviews were conducted with 22 participants (6 MJD patients, 7 nurses and 9 doctors) at the Mseleni hospital (Table 3.1). Interviewed patients and nurses were of mostly of female gender, and doctors were mostly of male gender (Table 3.1). The MJD patients were between 58-and 76-years old (one patient was younger than 65 years old).

3.3 Prevalence and distribution of MJD

A point prevalence of 9% ($n = 66/723$) was calculated for medical records sampled at the OPD of the Mseleni Hospital in May 2019. MJD was significantly associated with gender ($p=0.04$) and was prevalent in 11% of women (49/446) and 6% of men (17/277) (Table 3.4 and Figure 3.3A). The youngest patient with MJD was 37 years old and the oldest was 94 years old (Figure 3.3B). MJD was most prevalent in patients older than 71 years (26%, 22/89), followed by 61-70 years (19%, 14/75) and 51-60 years (18%, 21/117). The prevalence of MJD was greater in women than men regardless of age, with the most significant differences in the 41–50 year old and ‘70+’ years old groups (Figure 3.3B).

Gender and age were significantly associated with MJD, and women were nearly twice as likely to have MJD as men (OR = 1.89) (Table 3.4). As only one patient younger than 40 years with MJD was identified – all patients younger than 40 years were excluded from logistic regression analyses as their inclusion prevented the model from converging. Therefore, the youngest included age group (41–50 years) was selected as the reference group. Relative to the 41–50 years age group, the likelihood of detecting MJD increased approximately threefold in patients between 51-60 years (OR = 2.93) and 61-70 years (OR = 3.07). Individuals older than 70 years were four-times more likely to have MJD than the control group (OR = 4.60). While age is a significant risk factor for MJD in both men and women, women seeking care at the OPD for MJD were older than men (Figure 3.3C). Once age was corrected for in the model, the β -coefficient increased by more than 10%, indicating that age is a confounder of the association between MJD and gender (Table 3.5).

3.3.1 Geographic distribution of MJD

Approximately 89% (656/733) patients sampled from medical records at the OPD were from the uMkhanyakude municipal region. MJD patients were mostly from within the Mseleni Hospital catchment area, Umhlabuyalingana (86%, 57/66), with 6% (6/66) and 5% from nearby Big Five Hlabisa and Jozini districts, respectively (Table 3.4). Patients sampled in medical records at the OPD were most frequently from wards with close proximity to the Mseleni Hospital (Figure 3.3D). Three patients were from districts adjacent to uMkhanyakude (Figure 3.3E), and MJD was only detected in one of these individuals. When crude prevalence frequencies were plotted relative to global positioning system (GPS) co-ordinates of patient-reported addresses, the highest prevalence of MJD was identified within close proximity to the Mseleni Hospital (Figure 3.3E).

Table 3.3. Gender, age and geographic regions of residence recorded for patients with Mseleni Joint Disease (MJD) sampled in the medical record review at the Outpatients Department of the Mseleni Hospital in 2019.

| Variables | MJD positive | MJD negative | Total sample |
|---|-------------------|--------------------|------------------|
| | (n = 66) n (%) | (n = 657) n (%) | (n=723) n (%) |
| Gender[†] | | | |
| Women | 49 (11) | 397 (89) | 446 (62) |
| Men | 17 (6) | 260 (94) | 277 (38) |
| Age categories[‡] [years] | | | |
| 6-10 | 0 (0) | 18 (100) | 18 (3) |
| 11-20 | 0 (0) | 72 (100) | 72 (10) |
| 21-30 | 0 (0) | 115 (100) | 115 (16) |
| 31-40 | 1 (1) | 124 (99) | 125 (17) |
| 41-50 | 8 (7) | 107 (93) | 115 (16) |
| 51-60 [‡] | 21(18) | 96 (82) | 117 (16) |
| 61-70 [‡] | 14 (19) | 61(81) | 75 (10) |
| 71+ [‡] | 22 (26) | 64 (74) | 86 (12) |
| Geographic regions in uMkhanyakude | | | |
| Big Five Hlabisa | 6 (6) | 96 (94) | 102(15) |
| Jozini | 2 (5) | 38 (95) | 40 (6) |
| Mtubatuba | 0 (0) | 11 (100) | 11 (2) |
| Umhlabuyalingana [◊] | 57(10) | 510 (90) | 567 (78) |
| Adjacent areas | 1 (33) | 2(67) | 3 (0.4) |

MJD-Mseleni Joint Disease; n- number of individuals; % - percentage. Percentages calculated within rows. X² were used to assess the association between MJD, demographic and spatial variables. Local regions reported by patients.
[†]Significant association between MJD and gender: df (1), p=0.03; [‡] Significant association between MJD and age: df (5), p ≤0.0001; [◊]Significant association between Umhlabuyalingana and MJD: p <0.0001

Table 3.4 Logistic regression analyses of the association between Mseleni Joint Disease (MJD), risk factors (gender and age) for patients visiting the Outpatients Department at the Mseleni Hospital in May 2019.

| | n | β-coefficient | OR | OR 95% CI |
|-------------------------------------|-----|---------------|----------------|------------|
| Single logistic regression | | | | |
| Gender [†] | 723 | 0.65 | 1.89* | 1.08-3.44 |
| Age category [years] [‡] | 393 | | | |
| 41-50 | 115 | - | - | - |
| 51-60 | 117 | 1.07 | 2.93* | 1.28-7.31 |
| 61-70 | 75 | 1.12 | 3.07* | 1.24-8.08 |
| 70+ | 86 | 1.53 | 4.60*** | 2.06-11.57 |
| Multiple logistic regression | | | | |
| Gender [†] | 723 | 0.78 | 2.17* | 1.18-4.18 |
| Age category (years) [‡] | 393 | | | |
| 41-50 | 115 | - | - | - |
| 51-60 | 117 | 1.04 | 2.84* | 1.24-7.13 |
| 61-70 | 75 | 1.27 | 3.56** | 1.42-9.45 |
| 70+ | 86 | 1.62 | 5.04*** | 2.17-12.79 |

OR- Odds ratio; CI- confidence intervals; n- number of individuals. Single logistic regression models were computed for gender and age individually and multiple logistic regression models with age and gender in the same model.
*Significance levels: * ≤ 0.05, ** ≤ 0.01, *** ≤0.001; [†] Male gender was used as a reference group; [‡] Patients younger than 41 years were excluded from regression models. Age category 31-49 was used as a reference group.*

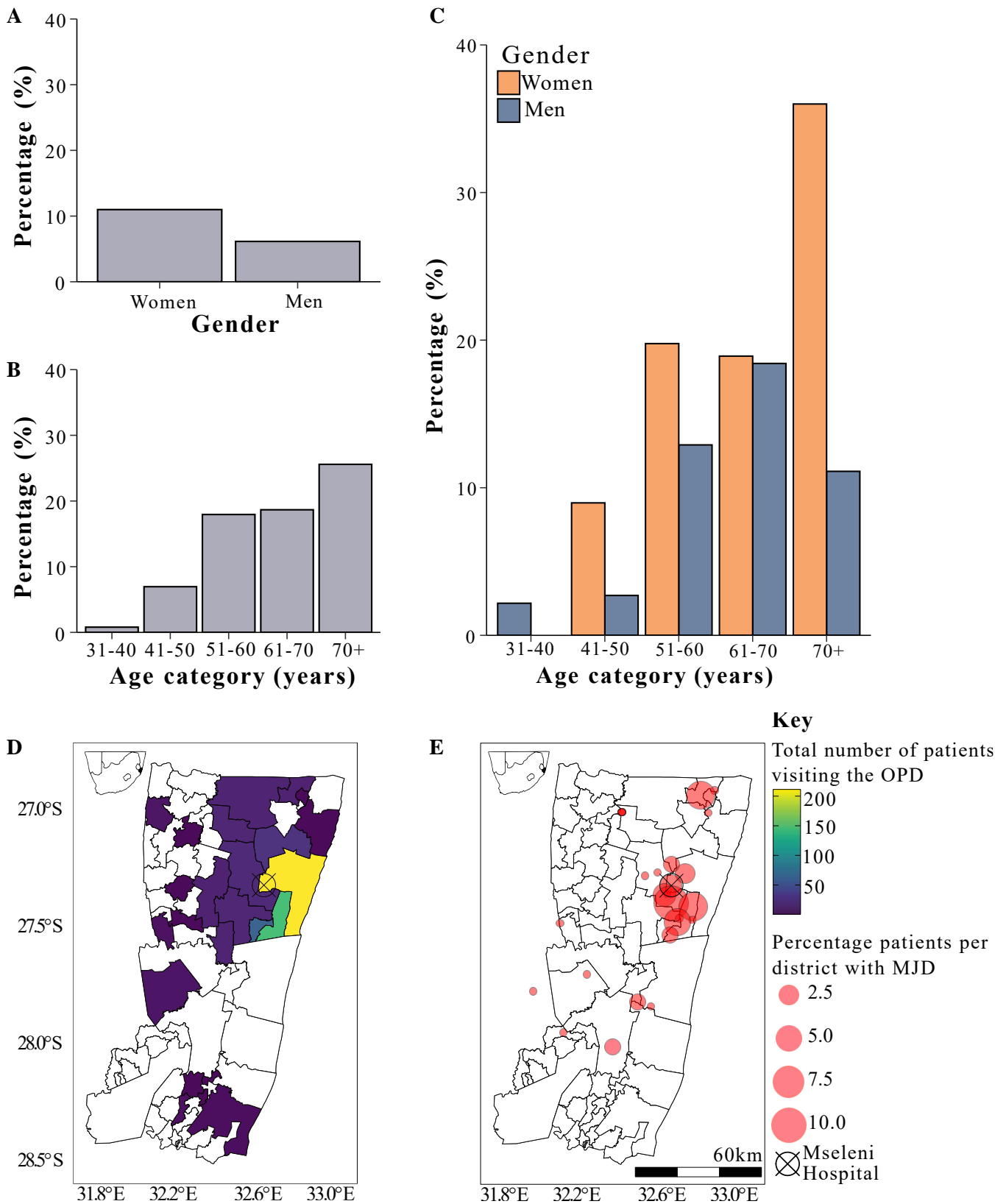


Figure 3.3 Demographic and geographic distribution of Mseleni Joint Disease (MJD) from the medical record review at the Outpatients Department (OPD) of the Mseleni Hospital in May 2019. (A) Percentage prevalence of MJD according to gender. (B) Percentage prevalence of MJD according to age categories. (C) Percentage prevalence of MJD according to gender and age categories. (D) Number of people visiting the OPD during the sampling period according to different municipal wards (E) Crude prevalence frequencies plotted relative to global positioning system (GPS) co-ordinates of patient-reported addresses.

Patients with MJD were largely from wards 2, 3, 12 and 15, and the highest prevalence per district was in ward 15 (Figure 3.5A). The northward localisation of more than 10 patients to district 12 and 17 was noted (Figure 3.4A). MJD patients were largely localised along the main tar and gravel roads (Figure 3.4B), nearby rivers (Figure 3.2C) and the largest clusters of patients were detected near the Mseleni Hospital (Figure 3.5C). The wards with the greatest prevalence frequencies of MJD (2, 3 and 15) did not have extensive water pipelines (see ward 1 and 17 for comparison) (Figure 3.4D). These data indicate detection of MJD in areas adjacent to transport routes and rivers, but with limited piped water access. The absence of precise addresses and GPS co-ordinates for all patients, prevented Euclidian distances between MJD patients and landmarks from being assessed.

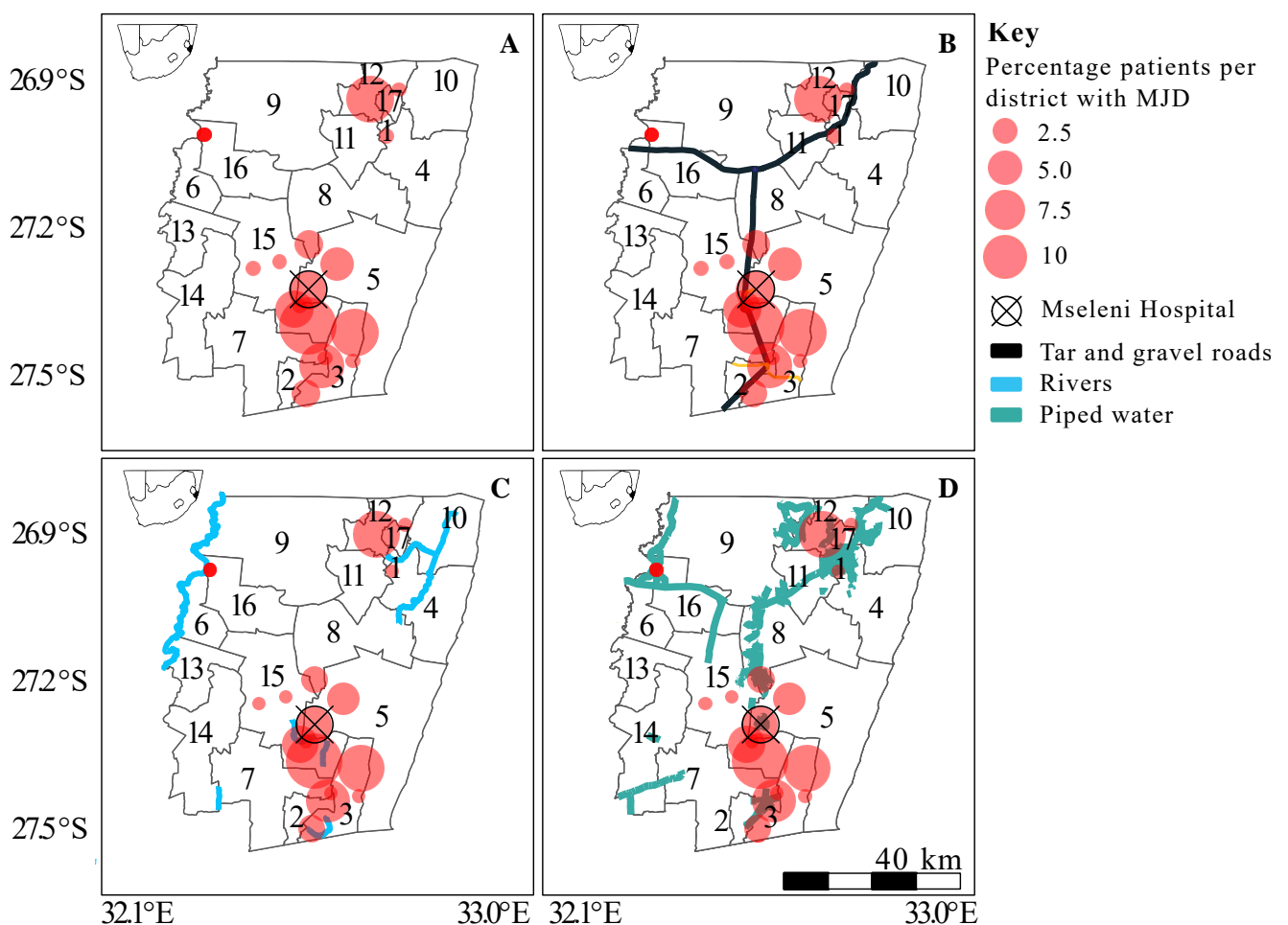


Figure 3.4 Spatial distribution of Mseleni joint disease in the Umhlabuyalingana local district from medical record reviews in 2019. Crude prevalence frequencies plotted relative to global positioning system (GPS) co-ordinates of patient-reported addresses (A), mapped relative to tar and concrete roads (B), rivers (C), piped water schemes (D).

3.3.2 Familial history of MJD

As a full-scale kinship analysis was beyond the scope of this study, a summary of MJD prevalence rates for different familial relations was calculated. Only three men were surveyed and only 2 reported a family history of MJD. One man reported MJD in a biological brother, while another reported MJD in his wife but not his adult children. Women cited MJD most frequently in relatives that were women rather than men (Figure 3.5), Approximately (29%) (11/37) of surveyed individuals reported MJD in their mothers, 19% (7/37) and 13% (5/37) in their biological sisters and brothers, respectively (Figure 3.5). Only 8% (3/37) of surveyed women noted MJD in their biological fathers, and in general, prevalence rates in grandparents on the paternal line were lower than in the maternal line (Figure 35). None of the surveyed women reported MJD in their daughters, but 6% (2/34) reported MJD in their sons.

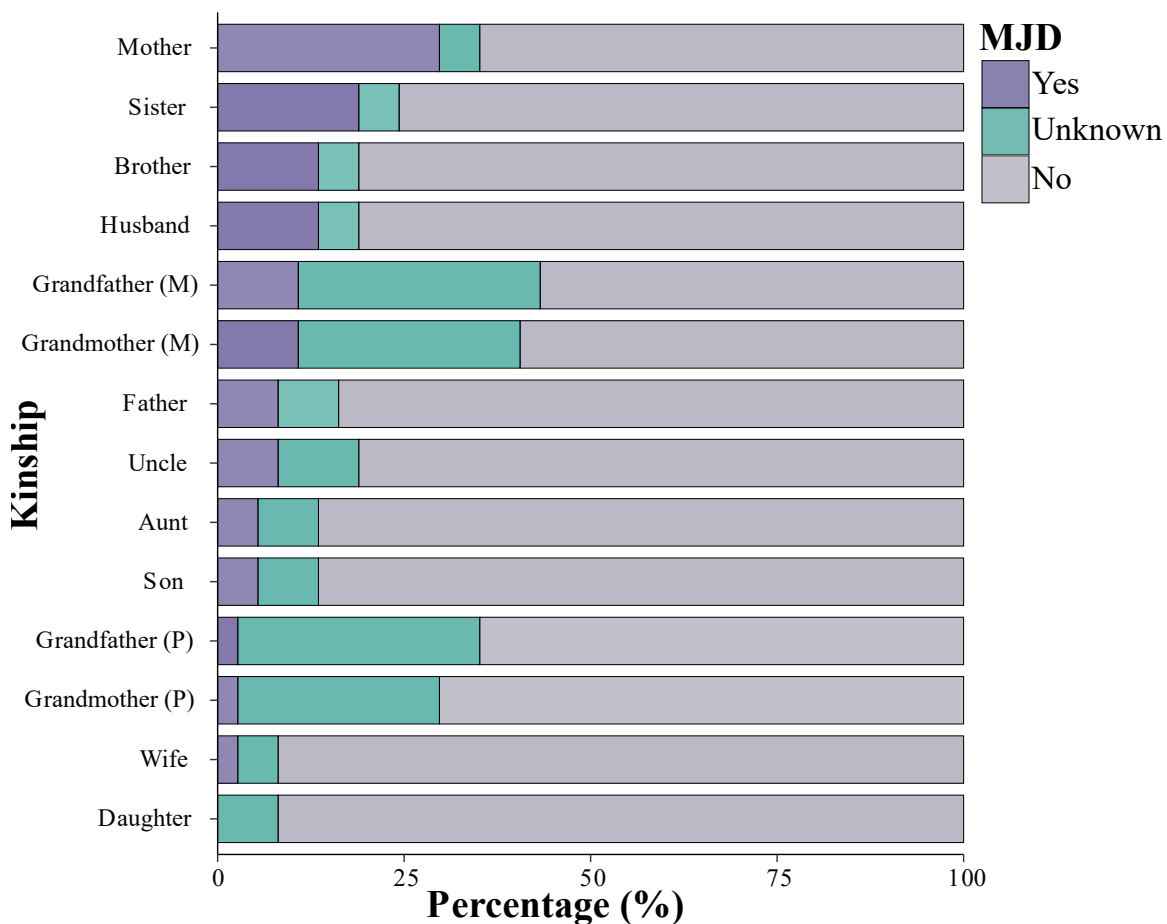


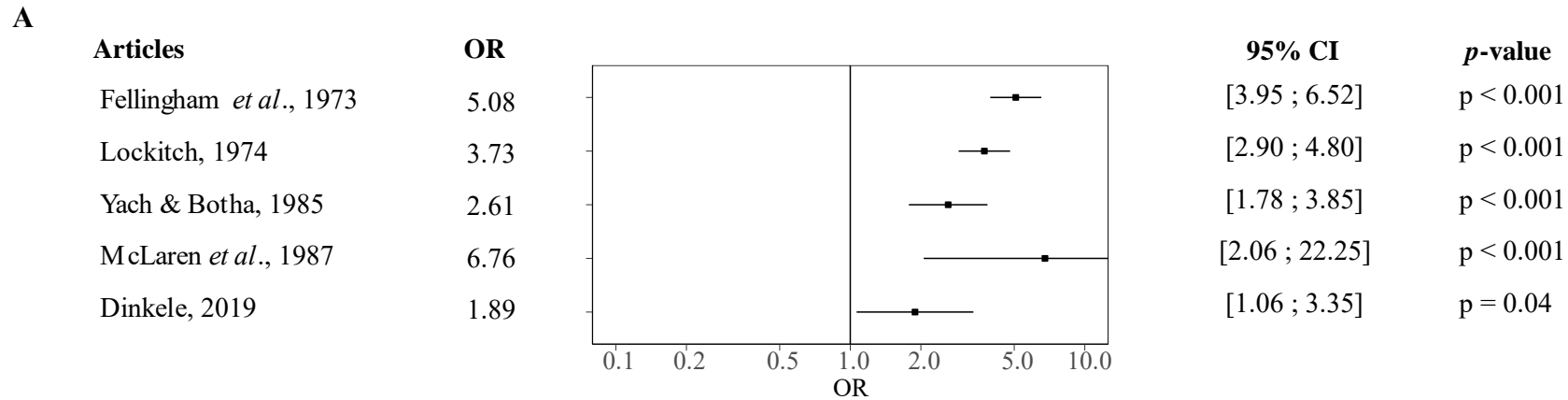
Figure 3.5 Family history of MJD plotted as prevalence frequencies per relative calculated in all surveyed patients.

3.3.3 Meta-analysis of the prevalence of MJD

Only 4 research articles satisfied criteria for inclusion in the meta-analysis (Fellingham *et al.* (1973); Lockitch (1974); Yach & Botha (1985) and McLaren *et al.* (1987))(Table 3.2). While all the above-mentioned studies had different sample sizes, each reported significant power to detect prevalence rates in their enumerated samples. Population-based prevalence surveys by Lockitch (1974) ($n=5031$), Yach and Botha (1985) ($n=2745$) and Fellingham *et al.* (1973) ($n=2015$) reported the largest sample sizes. Hospital based surveys by McLaren *et al.*, (1987) ($n=1659$) and our medical record review ($n=723$) reported the lowest sample sizes (Figure 3.6 A). There was a notable decline in prevalence estimates in the first three population-based surveys from 28% (1973), to 11% (1974) to 5% (1985) (Figure 3.6B).

In all studies included in the meta-analysis, MJD was significantly more prevalent in women than men (Figure 3.7 A and B). The odds of MJD in women detected by different studies declined temporally from 1973 (OR=5.08, CI=3.95-6.52; $p\leq 0.0001$) to 2019 (OR= 1.89, CI=1.06-3.33; $p=0.04$). Results from McLaren *et al.*, (1987) were the exception as, as a 7-fold increased likelihood of MJD was detected in women (OR=6.76, CI=2.06-22.25; $p\leq 0.0001$) sampled. As evidenced by the broad 95% confidence intervals, this result should be interpreted with caution as only 3 men with MJD were sampled, and this may bias the strong association between female gender and MJD (Figure 3.7A).

Broad age categories corresponding to data reported by Fellingham *et al.*, 1973 were used to assess age as a risk factor of MJD. A minor difference of one year between age categories used by Fellingham *et al.*, 1973 (0-29 years) and Yach and Botha (1985) (0-30 years) was identified, but this was not deemed significant enough to result in meaningful differences between age categories during comparison. The prevalence of MJD increased with age, with highest prevalence noted in those more 50 years old (Table D6). Odds ratios were calculated by using the 30-50 year old group as a reference because this was the youngest age group affected with MJD across all studies. The trends in Figure 3.8 suggest an increased likelihood of MJD in people over 50 years-of-age. Once again, McLaren *et al.*, (1987) appeared as an outlier to the overall temporal trends in the odds of MJD. The likelihood of MJD in older age groups was significantly higher in studies from 2019-1973 (excluding McLaren *et al.*, (1987)) (Figure 3.7). Our study was the only study not to detect MJD in those under the age of 29 years old.



B

| Articles | MJD positive | | MJD negative | | Total <i>n</i> | Prevalence % |
|--|--------------|--------------|--------------|--------------|-------------------|-----------------|
| | Women | Men | Women | Men | | |
| | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | | |
| Fellingham <i>et al.</i> , (1973) [‡] | 480 (39) | 87 (11) | 754 (61) | 694 (89) | 2015 | 28 |
| Lockitch (1974) [‡] | 46 (13) | 74(4) | 2825 (86) | 1663 (96) | 5031 | 11 |
| Yach and Botha (1985) [‡] | 116 (7) | 35 (3) | 1450 (93) | 1144 (97) | 2745 | 5 |
| McLaren <i>et al.</i> , (1987) [†] | 30 (8) | 3 (0.4) | 970 (97) | 656 (100) | 1659 | 2 |
| Dinkele (2019) [†] | 49 (11) | 17(6) | 397 (89) | 260 (94) | 723 | 9 |

MJD-Mseleni Joint Disease; n - number of individuals; % - percentage. Percentages calculated within rows; † Hospital-based surveys; ‡ Population based-surveys.

Figure 3.6 Frequency distribution and forest plots of the association between MJD and gender for studies identified in the meta-analysis, and results from the 2019 hospital-record review. Graphical depictions of odds ratios (OR) and 95% confidence intervals (95% CI) of MJD prevalence in females depicted using black boxes and black lines, respectively. The p-value for odds ratios are also given. Due to the heterogeneity in study designs, a combined OR estimate was not calculated.

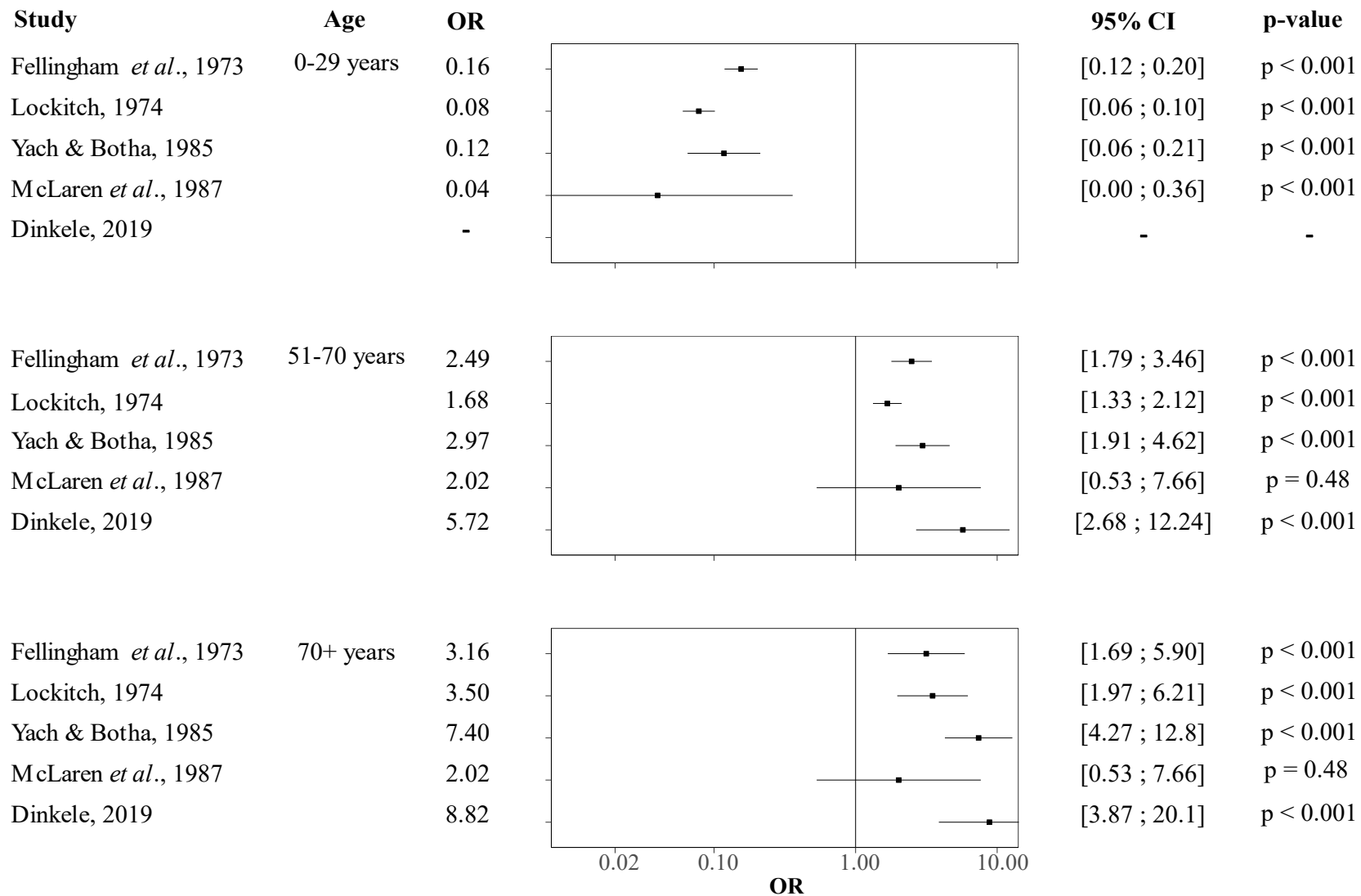


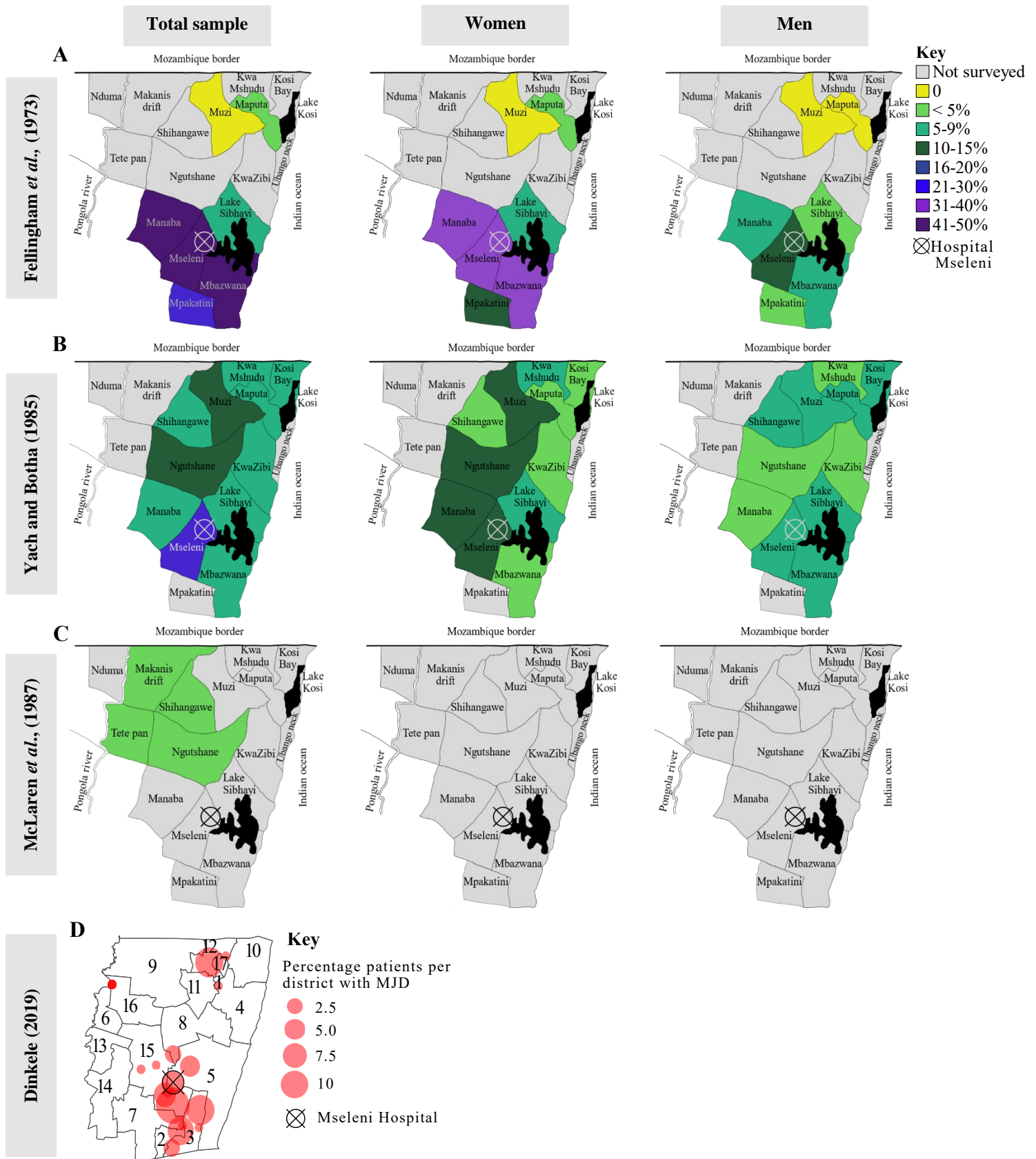
Figure 3.7 Forest plots of the association between Mseleni joint disease (MJD) and age for studies identified in the meta-analysis, and results from the 2019 hospital-record review. (Graphical depictions of odds ratios (OR) and 95% confidence intervals (95% CI) of MJD prevalence in different age categories depicted using black boxes and black lines, respectively. The p-value for odds ratios are also given. Due to the heterogeneity in study designs, a combined OR estimate was not calculated.

To assess the geospatial localisation of MJD from meta-analysis data, the prevalence frequencies for the surveyed regions were plotted using maps from (McLaren *et al.*, 1987). Geographic data from Lockitch (1974) was not plotted as these data were published in Fellingham *et al.* (1973). The geospatial ward demarcations used in our study (Figure 3.4) did not correspond to those used in previous studies. Yach and Botha (1985) sampled a wider geographic area than Fellingham *et al.* (1973) and identified affected areas northwards of the Mseleni Hospital in Kosi Bay, Maputa, Muzi and Shihangawe (Figure 5.4). The highest prevalence was detected in three regions adjacent to the Mseleni Hospital – Mseleni, Manaba and Mbazwana (Figure 3.8, Table 3). The prevalence patterns detected by Yach and Botha (1985) and Fellingham *et al.* (1973) resemble those detected in our medical records reviews. Fellingham *et al.* (1973) (Figure 3.9) did not identify any cases of MJD in Muzi, but 16-20% of individuals sampled by Yach and Botha (1985) in Muzi had MJD. McLaren detected MJD in Tete Pan and Makani’s drift (McLaren *et al.*, 1987). Overall, MJD was more prevalent among women than men, and this trend remained constant for each spatial region (Figure 3.9).

Table. 3.5 Frequency distribution of Mseleni joint disease (MJD) per geographic region and gender for studies by Fellingham *et al.* (1973); Yach & Botha (1985); McLaren *et al.* (1987) included in the meta-analysis.

| | MJD positive females (%) | | | MJD positive males (%) | | | Total MJD (%) | | |
|---------------|--------------------------|-------------------|-------------------|------------------------|-------------------|-------------------|---------------|-------------------|-------------------|
| | 1973‡ | 1985 ^o | 1987 [†] | 1973‡ | 1985 ^o | 1987 [†] | 1973‡ | 1985 ^o | 1987 [†] |
| Kosi Bay | - | < 5 | - | - | < 5 | - | - | 5-10 | - |
| KwaMshudu | - | 5 | - | - | < 5 | - | - | 5-10 | - |
| KwaZibi | - | < 5 | - | - | 5 | - | - | 5-10 | - |
| Lake Sibhayi | 6 | 5 | - | 0.5 | < 5 | - | 6 | 5-10 | - |
| Makanis drift | - | - | - | - | - | - | - | - | 0.3 |
| Manaba | 39 | 15 | - | 8 | 5 | - | 47 | 20 | - |
| Maputa | 3 | < 5 | - | 0 | < 5 | - | 3 | 5-10 | - |
| Mbazwana | 39 | < 5 | - | 8 | < 5 | - | 47 | 5-10 | - |
| Mphakatini | 15 | - | - | 3 | - | - | 18 | - | - |
| Mseleni | 39 | 15 | - | 11 | 6 | - | 50 | 21 | - |
| Muzi | 0 | 10 | - | 0 | < 5 | - | 0.0 | 15-20 | - |
| Ngutshane | - | 10 | - | - | 5 | - | - | 15 | 4 |
| Shihangawe | - | < 5 | - | - | < 5 | - | - | 5-10 | 3 |
| Tete Pan | - | - | - | - | - | - | - | - | 1 |

MJD-Mseleni Joint Disease; % - percentage. Percentages obtained from papers by Fellingham *et al.*, (1973)[‡]; Yach and Botha (1985)^o; McLaren *et al.*, (1987)[†]. Lockitch (1974) reported geographic prevalence rates of Fellingham *et al.*, (1973).



3.4 Pathology and onset of MJD

Period of onset was only assessed from survey responses of MJD patients as this information was not recorded in medical records. The average onset age of MJD in surveyed patients was 42 years (± 17 years). Approximately, 56% (20/37) described onset relative to an age or year while 28% (10/37) described onset relative to stage of life, and 17% (6/37) according to a significant life event (Figure 3.9A-B). Patients with shorter disease durations were more likely to describe MJD according to age and year, while patients with disease durations of more than 16 years described onset relative to life stages (for example 'youth', 'adulthood' or 'childhood') (Figure 3.9 A-B). Childbirth and working in a different city were most frequently cited life events, while 'childhood' or 'adulthood' were most frequently used life stages used to describe onset.

Disease duration was calculated as the time-since-diagnosis from the sampling period (2019). Surveyed patients with shorter disease durations (0-5 years) mostly reported unilateral joint immobility and pain during surveying, in contrast to patients with longer disease durations (10-15 years) who most commonly reported bilateral immobility (Figure 3.9C). This correlated with medical records of MJD patients (Figure 3.9D), suggesting that the pattern of pathology progresses to bilateral immobility as the time-since onset progresses. This is suggestive of a high prevalence of disability in MJD patients with longer disease durations.

Trends in the pattern of pathology from surveys were consistent with assessments of pathology from medical records at the Mseleni Hospital. The onset of pain occurred exclusively in the appendicular skeleton and was mostly unilateral (Figure 3.11-3.12 and Table D7). Approximately 68% (25/37) of surveyed MJD patients reported pain onset in the hip, and this occurred unilaterally (54%; 20/37) more frequently than bilaterally (14%; 5/37) (Figure 3.10). Onset in the hip and knee joint was also most common in medical records (Figure 3.11). When joint pathology at onset and present (at sampling) were stratified according to disease duration, hip and knee joints had the greatest prevalence of bilateral pain (Figure 3.11-3.12; Table D7). Only 5% (2/37) of survey respondents reported shoulder joints affected and 10% (4/37) noted forearm joints affected at onset (Table D7). Patients who were unsure of their duration of disease reported bilateral hip and knee pathology, similar to patients with longer disease durations (Figure 3.11). Lumbar pathology was identified more frequently in medical records and surveys of patients with disease durations of more than 5 years (Figure 3.10-3.12). An association between age and stage of disease was detected and individuals with bilateral immobility were older than those with both unilateral immobility ($p=0.02$) and only joint pain ($p=0.02$). MJD age distribution was assessed according to disease duration and staging, individuals who suffered from MJD for more than 5 years were significantly older ($p<0.0001$), and furthermore, bilateral immobility most affected individuals above the age of 60.

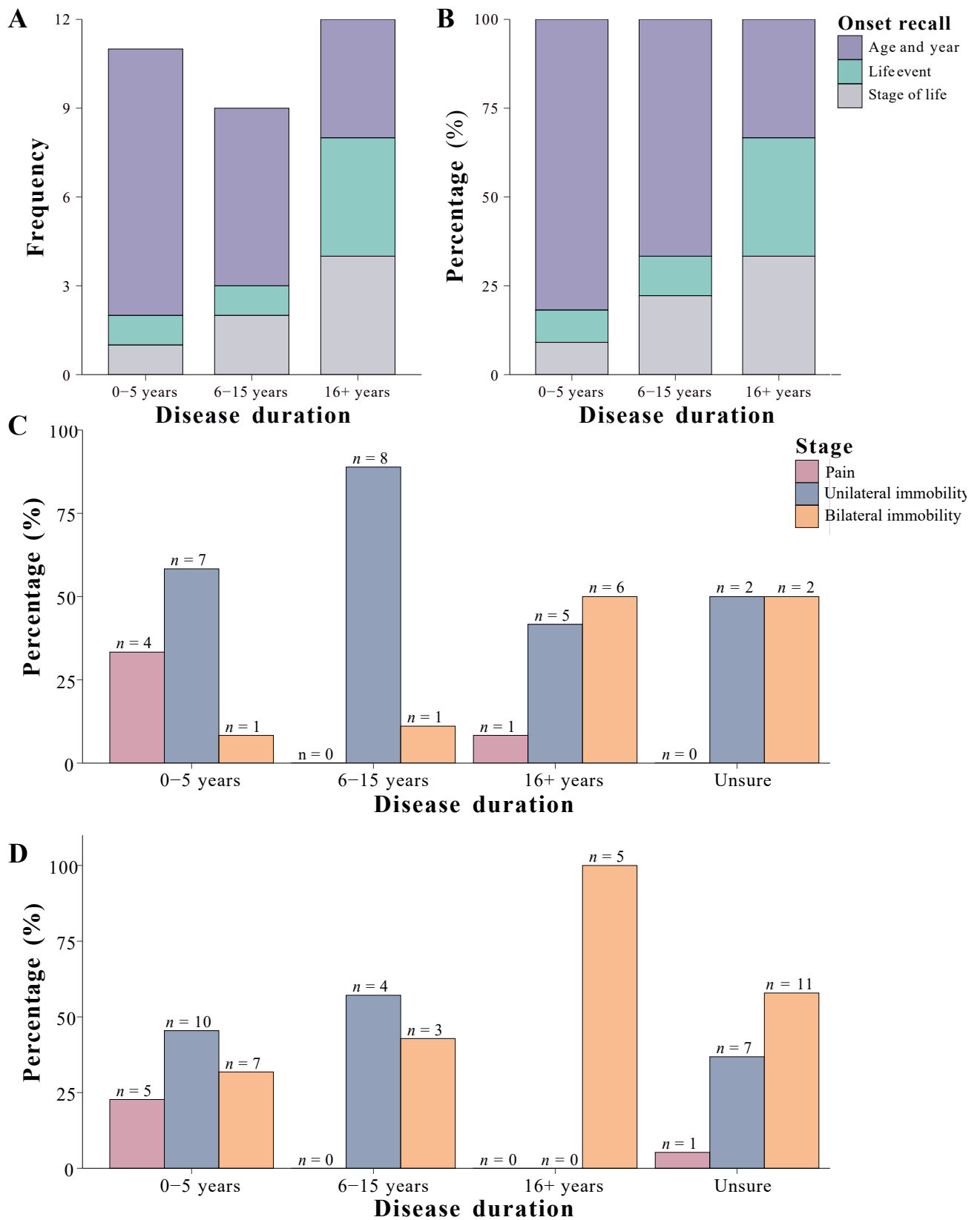


Figure 3.9 Mseleni Joint Disease (MJD) onset recall, and symptoms present at sampling relative to disease duration assessed from medical record reviews and surveys. Frequency (A) and percentage (B) onset recall from surveyed MJD patients with different disease durations. Onset recall was categorised according commonly occurring responses: age and year (ages, dates and times), life events (childbirth, employment, moving cities) and stages of life ('youth', 'adulthood' and 'childhood'). Symptoms (at sampling) reported by patients from surveys (C) and recorded in medical record reviews (D) plotted relative to disease durations.

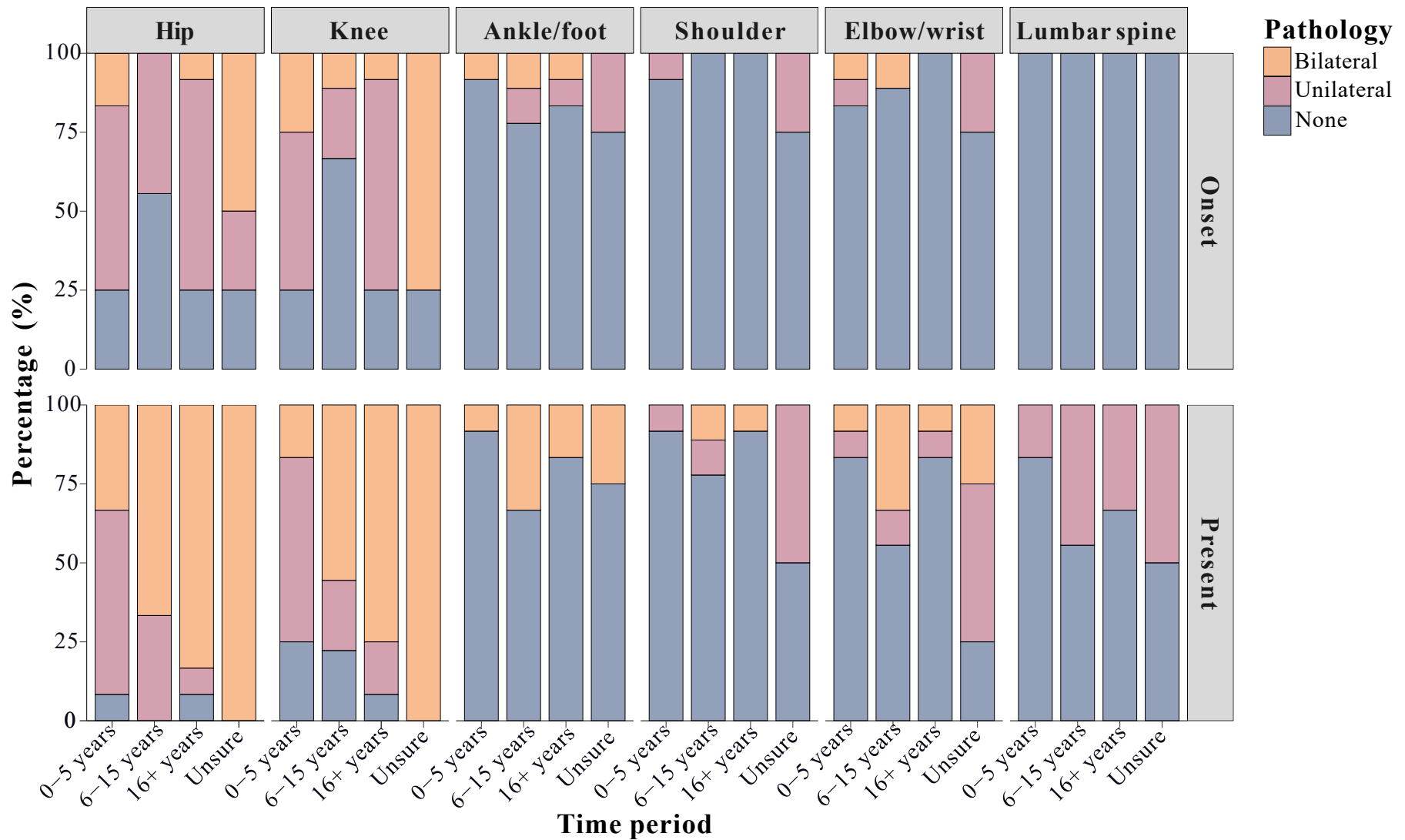


Figure 3.10 Percentage frequencies of joints affected by bilateral and unilateral pain at onset and during the sampling period by surveyed patients with Mseleni Joint Disease (MJD).

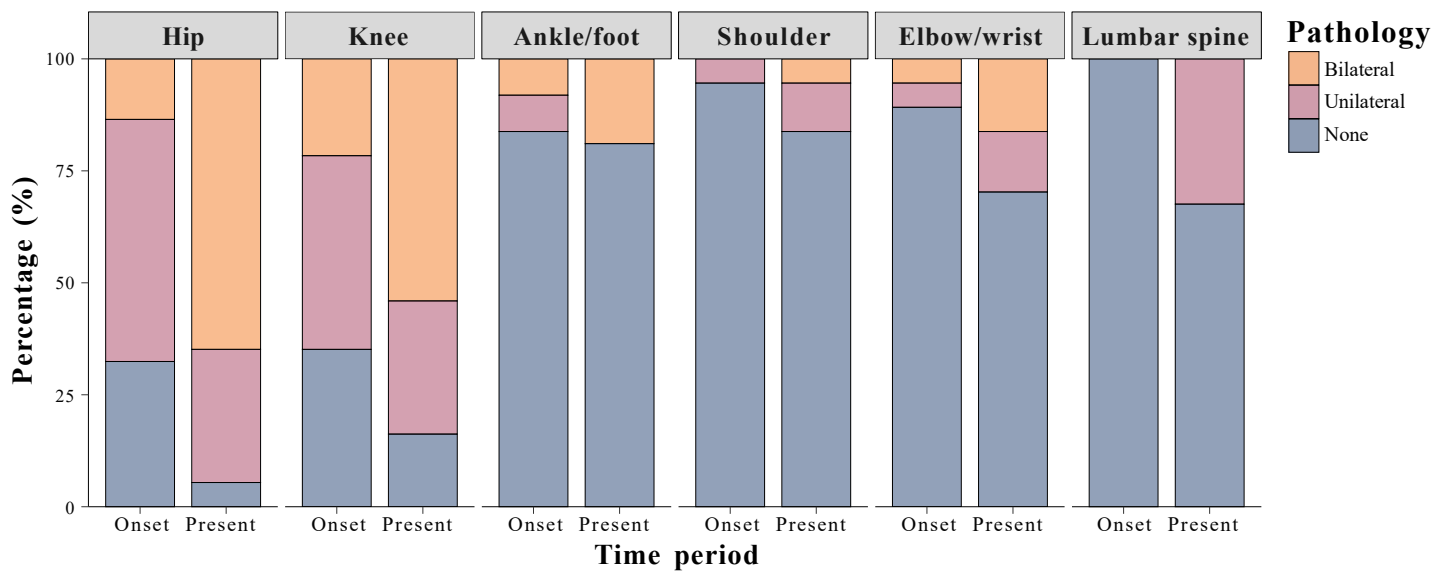


Figure 3.11 Frequency of pathology recorded at onset and present at sampling for joints recorded in medical records of patients with Mseleni Joint Disease (MJD).

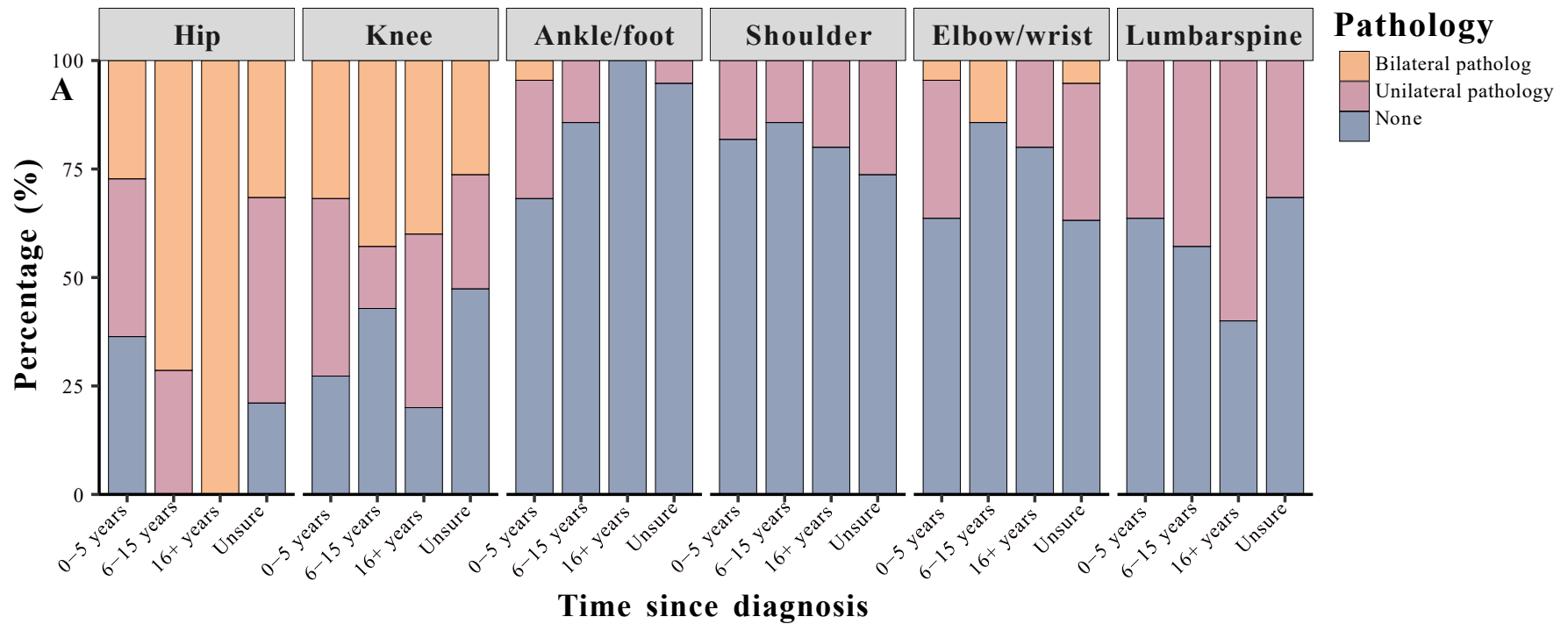
3.4.1 Co-morbidities associated with MJD

Brachydactylous dwarfism was not recorded in any of the reviewed medical records and only two dwarfed women, aged 60 and 62, with MJD were surveyed. No significant differences in responses were identified between these patients and participants of average stature. Inconsistent record keeping and lack of measurements of patients in medical records, prevented the use of stature to identify brachydactylous dwarfism. Overall, from medical records and surveys, no co-morbidities were associated with MJD.

3.5 Diagnosis and treatment of MJD

The absence of a standardised diagnostic protocol to assess the presence of MJD was apparent from medical records, and inconsistencies in the recording of pathology and diagnostic assessments limited clinical analyses. Records taken by clinicians rarely noted an absence of pathology, despite X-rays or assessments requested. All patients' had evidence of X-Ray diagnoses of MJD, with little written about pathological indications in the radiographs. Notably, neither MED nor protrusio acetabuli were recorded in medical records.

It was, however, possible to identify limited range of movement in the hips and knees for 83% (44/53) (Table 3.6). Radiating leg pain between the hip and knee was recorded in the medical records of 58% (31/53) of MJD patients (Table 3.6). Crepitus was recorded as a symptom for 5/53 patients, while the remaining records lacked evidence of crepitus or the assessment of crepitus.



B

| | Hip | | Knee | | Ankles/feet | | Shoulders/ elbows/wrists | | Elbows | | Wrists/hands | | Lumbar spine | |
|------------------|-----|----|------|----|-------------|----|-----------------------------|----|--------|----|--------------|----|--------------|----|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| Present | 41 | 77 | 34 | 64 | 12 | 23 | 11 | 21 | 4 | 8 | 8 | 15 | 20 | 38 |
| Right | 15 | 28 | 12 | 23 | 6 | 11 | 7 | 13 | 1 | 2 | 4 | 8 | - | - |
| Left | 4 | 8 | 5 | 9 | 3 | 6 | 4 | 8 | 3 | 6 | 1 | 2 | - | - |
| Bilateral | 22 | 42 | 17 | 32 | 3 | 6 | - | - | - | - | 3 | 6 | - | - |
| No record | 12 | 23 | 19 | 36 | 41 | 77 | 42 | 79 | 49 | 92 | 45 | 85 | 33 | 62 |
| Total | 53 | | 53 | | 53 | | 53 | | 53 | | 53 | | 53 | |

MJD-Mseleni Joint Disease; n- number of individuals; % - percentage. Percentages calculated within columns

Figure 3.12 Percentage frequencies of joints affected by bilateral and unilateral pain at during the sampling period identified from medical records and stratified by disease duration

Approximately, 40% (21/52) of MJD patients visiting the OPD reported new sources of pain and 21% (11/52) were given prescription renewals for analgesia (Table D3). Survey respondents (79%) reported use of NSAIDS for pain management which corresponded with prescriptions of pain medication in medical records (87%) (Table 3.6). Non-adherence to physiotherapy was common (46%, 17/37) and no significant associations were detected between age and adherence to treatment (Table 3.6). Approximately 23% (12/53) of MJD-patients from the medical record reviews had a single joint replacement, while 6% (2/52) had multiple operations including revision surgeries (Table 3.6). A negative association was identified between joint arthroplasties and age ($p=0.03$), as older patients sampled in the medical record review were less likely to undergo surgery. The group that refused surgery ($p=0.005$) and the group that had surgery were both significantly older than the group with evidence of surgical referral in their medical records ($p=0.002$).

Table 3.6 Frequency distributions of clinical assessments, symptoms and treatment of Mseleni joint disease (MJD) reported by surveyed patients and recorded in medical records.

| | | | Medical records | Surveys |
|----------------------------|-----------------------------|--------------------------------|------------------------|----------------|
| | | | <i>n</i> (%) | <i>n</i> (%) |
| Symptoms at present | Range of movement | Limited | 44 (83) | - |
| | | Full | 9 (17) | - |
| | Swelling | Present | 8 (15) | - |
| | | Absent | 40 (76) | - |
| | Radiating leg pain | Present | 31 (59) | - |
| | | Absent | 13 (25) | - |
| Treatments | Physiotherapy | Yes | 41 (78) | 11 (30) |
| | | Non-adherence | 1 (2) | 17 (46) |
| | | None | 11 (21) | 9 (24) |
| | Pharmacological | NSAIDs | 52 (98) | 29 (78) |
| | | Topical | 1 (2) | 3 (8) |
| | | None | 0 | 5 (14) |
| | Surgical[‡] | Total joint arthroplasty (TJA) | 12 (23) | 6 (15) |
| | | Multiple TJAs | 4 | 2 (6) |
| | | Non-adherence | 4 (8) | 12 (32) |
| | | Operation scheduled | 4 (8) | 0 |
| | No referral | 29 (55) | 7 (19) | |

n- number of individuals; % - percentage. Percentages calculated within columns [‡]No answer provided by 11 patients in surveys

3.6 Socio-ecological risk factors of MJD

A total of 99 patients (45 MJD-affected and 44 MJD-unaffected) were surveyed at the OPD of the Mseleni Hospital. More women ($n=79$) than men ($n=20$) were sampled (Table 3.7). The median age of the sample was 55 years \pm 26 years ($p=0.79$) (Table 3.7). MJD patients were more likely to be women ($p=0.005$) and older than 30 years of age ($p=0.0001$). For the purposes of this survey, the “past” was defined as a least 10 years prior to the sampling period. The majority of survey participants were from ward 3, 5 and 8 (near the Mseleni Hospital) and no significant geographic localisation of MJD was notable (Figure 3.13).

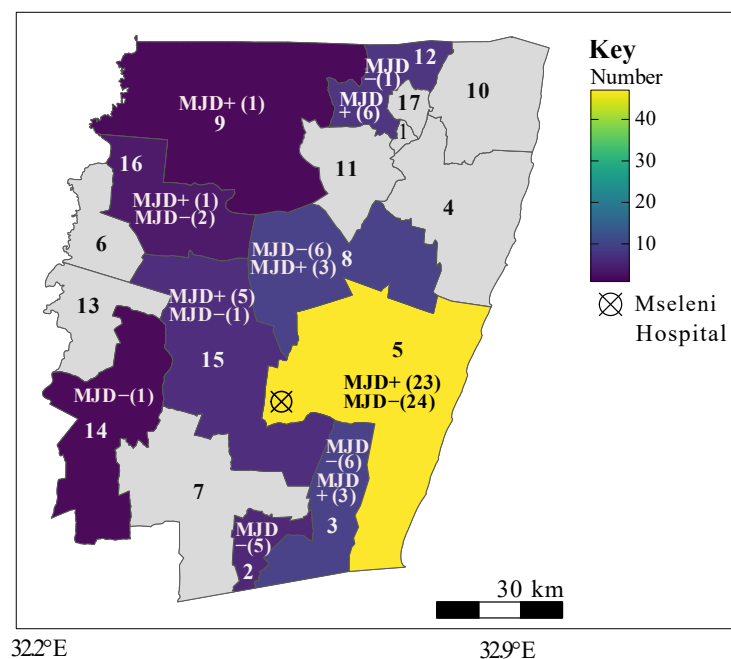


Figure 3.13 Geographic distribution of Mseleni Joint Disease (MJD) assessed from surveys of MJD-affected and unaffected individuals at the Mseleni Hospital. Crude prevalence of MJD positive (+) and MJD (-) participants plotted relative to the total number of individuals sampled per ward.

No significant association was detected between MJD and water source in the past and present, food source in the past, dwelling type in the present or access to electricity in the past (Table 3.7). MJD was significantly associated with limited access to monetary income, public transport, and formal dwellings in the past (Table 3.7-3.8). MJD-affected individuals were more likely to rely on subsistence farming than monetary income or a combination of both in the past ($p \leq 0.0001$). Approximately 40% (19/47) of MJD-affected individuals were receiving pension grants during sampling, and 46% (22/47) were employed during the survey period. Improved access to public transport and electricity was reported in MJD affected and unaffected individuals (Table 3.7).

Table 3.7 Demographics and lifestyle conditions assessed from surveys of MJD-affected and unaffected individuals at the Mseleni Hospital.

| | MJD positive | | MJD negative | | <i>p</i> -value |
|-------------------------------|--------------|----|--------------|-----|-----------------|
| | <i>n</i> | % | <i>n</i> | % | |
| Gender | | | | | 0,005 |
| Women | 42 | 53 | 37 | 47 | |
| Men | 3 | 15 | 17 | 85 | |
| Age [years] ‡ | | | | | 0,0001 |
| 19-30 | 7 | 24 | 22 | 76 | |
| 31-50 | 21 | 64 | 12 | 36 | |
| 51-65 | 16 | 64 | 9 | 36 | |
| 66-89 | 1 | 25 | 3 | 75 | |
| Water source [past] | | | | | 0,90 |
| Household tap | 2 | 67 | 1 | 33 | |
| Community access point | 19 | 50 | 19 | 100 | |
| River | 21 | 45 | 26 | 55 | |
| Water source [present] | | | | | 0,78 |
| Household tap | 35 | 45 | 42 | 55 | |
| Community access point | 8 | 50 | 8 | 50 | |
| River | 1 | 25 | 3 | 75 | |
| Food source [past] | | | | | ≤ 0,0001 |
| Subsistence farming | 37 | 62 | 23 | 38 | |
| Mixed | 6 | 25 | 18 | 75 | |
| Monetary | 1 | 8 | 12 | 92 | |
| Food source [present] | | | | | |
| Subsistence farming | - | - | 2 | 100 | 0,43 |
| Mixed | 30 | 45 | 36 | 55 | |
| Monetary | 14 | 47 | 16 | 47 | |
| Transport [past] | | | | | 0,01 |
| Public transport | 3 | 16 | 16 | 84 | |
| Walking | 41 | 53 | 37 | 47 | |
| Transport [present] | | | | | 0,05 |
| Privately owned cars | 3 | 20 | 12 | 80 | |
| Public transport | 39 | 52 | 36 | 48 | |
| Walking | 2 | 29 | 5 | 71 | |
| Dwelling [past] | | | | | 0,02 |
| Formal | 14 | 88 | 2 | 13 | |
| Traditional | 29 | 48 | 31 | 52 | |
| Informal | 11 | 50 | 11 | 50 | |
| Dwelling [present] | | | | | 0,47 |
| Formal | 39 | 46 | 46 | 54 | |
| Traditional | 2 | 67 | 1 | 33 | |
| Informal | 3 | 30 | 7 | 70 | |
| Employment [present] | | | | | 0,05 |
| Yes | 22 | 36 | 39 | 64 | |
| No | 4 | 50 | 4 | 50 | |
| Social grants | 19 | 63 | 11 | 37 | |
| Electricity [present] | | | | | 0,44 |
| Yes | 32 | 58 | 44 | 42 | |
| No | 11 | 45 | 9 | 55 | |

n - number of individuals; % - percentage. The "past" was defined as a least 10 years prior to the sampling period. Categories for dwelling type and water source from census publications. "Mixed" food source refers to subsistence and monetary income. Dwelling type is defined based on building materials used: "Formal" dwellings are built with concrete foundations and walls, "Traditional" dwellings with mud, bricks and sticks; "Informal" dwellings with iron, wood or other non-durable materials, and have no formal foundations.

Table 3.8 Logistic regression analyses of the association between Mseleni Joint Disease (MJD), demographic factors and lifestyle conditions assessed from surveys of MJD-affected and unaffected individuals at the Mseleni Hospital.

| | Unadjusted † | | | Adjusted † | | |
|-------------------------------|----------------------|----------------|-------------------|----------------------|---------------|-------------------|
| | β -coefficient | OR | OR 95% CI | β -coefficient | OR | OR 95% CI |
| Gender | 1.86 | 6.43* | 1.97-29.13 | 2.30 | 9.94** | 2.69-50.08 |
| Age [years] ‡ | 0.06 | 1.06*** | 1.03-1.10 | - | - | - |
| Water source [past] | | | | | | |
| Household tap | - | - | - | - | - | - |
| Access point | -0.78 | 0.46 | 0.02-5.10 | -0.14 | 0.32 | 0.01-6.00 |
| River | -0.91 | 0.40 | 0.02-4.50 | -0.12 | 0.34 | 0.01-6.37 |
| Water source [present] | | | | | | |
| Household tap | - | - | - | - | - | - |
| Access point | 0.18 | 1.20 | 0.40-3.58 | 0.28 | 1.32 | 0.39-4.49 |
| River | -0.92 | 0.40 | 0.02-3.28 | -1.05 | 0.35 | 1.03-1.10 |
| Food source [past]⁴ | | | | | | |
| Subsistence farming | - | - | - | - | - | - |
| Mixed | -1.58 | 0.21** | 0.07-0.57 | -1.00 | 0.37 | 0.11-1.14 |
| Monetary | -2.96 | 0.05** | 0.003-0.29 | -2.23 | 0.11* | 0.01-0.67 |
| Transport [past] | | | | | | |
| Public transport | - | - | - | - | - | - |
| Walking | 1.78 | 5.91** | 1.79-26.88 | 1.45 | 4.28* | 1.13-21.35 |
| Transport [present] | | | | | | |
| Privately owned cars | - | - | - | - | - | - |
| Public transport | 1.47 | 4.33* | 1.26-20.16 | 1.69 | 5.43* | 1.41-27.67 |
| Walking | 0.47 | 1.60 | 0.18-12.92 | 0.78 | 2.17 | 0.19-22.15 |
| Dwelling [past] | | | | | | |
| Formal | - | - | - | - | - | - |
| Traditional | 2.01 | 7.48* | 1.88-50.33 | 1.19 | 3.29 | 0.71-23.75 |
| Informal | 1.94 | 7.00* | 1.49-51.70 | 1.55 | 4.70 | 0.87-37.42 |
| Dwelling [present] | | | | | | |
| Formal | - | - | - | - | - | - |
| Traditional | 0.86 | 2.36 | 0.22-51.90 | 1.02 | 2.76 | 0.19-74.12 |
| Informal | -0.68 | 0.51 | 0.10-1.95 | -0.68 | 0.50 | 0.09-2.33 |
| Employment [past] | | | | | | |
| Yes | - | - | - | - | - | - |
| No | -0.39 | 0.68 | 0.30-1.53 | -0.22 | 0.80 | 0.32-1.99 |
| Employment [present] | | | | | | |
| Yes | - | - | - | - | - | - |
| No | 0.57 | 1.77 | 0.39-8.18 | -0.20 | 0.83 | 0.14-4.78 |
| Social grants | 1.12 | 3.06* | 1.25-7.79 | -0.31 | 0.74 | 0.20-2.56 |
| Electricity [past] | | | | | | |
| Yes | - | - | - | - | - | - |
| No | 0.52 | 1.68 | 0.62-4.63 | 0.54 | 1.72 | 0.56-5.49 |

OR- Odds ratio; CI- confidence intervals. Significance levels: * ≤ 0.05 , ** ≤ 0.01 , *** ≤ 0.001 . For the purposes of this survey, the “past” was defined as a least 10 years prior to the sampling period. The following were used as reference categories: male (gender); tap water (water source); subsistence farming (past food source); public transport (past transport); private car (present transport); cement (present and past housing); yes (employment past and present); yes (electricity). The “past” was defined as a least 10 years prior to the sampling period. Categories for dwelling type and water source from census publications. “Mixed” food source refers to subsistence and monetary income. Dwelling type is defined based on building materials used: “Formal” dwellings are built with concrete foundations and walls, “Traditional” dwellings with mud, bricks and sticks; “Informal” dwellings with iron, wood or other non-durable materials, and have no formal foundations. † Unadjusted odds ratios from single logistic regression analyses computed for all variables individually, adjusted odds ratios from multiple logistic regression analysis, controlling for the effect of age on all variables; ‡ Age was included as a continuous variable; ⁴ Only present food source was included in regression as past food source lacked significant variation.

Results from logistic regression show gender and age were significantly associated with MJD, and women were nearly seven times as likely to have MJD than men (OR= 6.43, CI=1.97-29.13; $p=0.01$) (Table 3.8). A multivariate logistic regression analysis was computed to test the association between MJD, sex and age. Once age was corrected for in the model, the odds ratio of MJD in women increased from 6.43 to 9.94 and the β -coefficient increased by more than 10% (Table 3.8), indicating that age is a confounder of the relationship between MJD and gender. The association between MJD and walking as a primary mode of transport in the past decreased once age was corrected for, suggesting the association between walking and MJD may be due to age (Table 3.8). The small sample of individuals using other forms of transport in the past (public transport and privately owned cars) may have skewed this result. Once age was corrected for, dwelling type in the past was no longer significantly associated with MJD.

The census data (1996-2011) suggested improved access to piped water in wards 3,5 and 15 and limited improvement of access in wards 12 and 17. Wards 3,5, 12, 15 and 17 had the highest crude prevalence rates detected in the medical records (Figure 14A and C). Improved access to formal housing and dwellings were reported from 1996-2011, this correlates with the increase in formal dwellings reported by surveyed participants over the previous ten years (Figure 1.14 B). Higher employment rates were detected in Umhlabuyalingana from 1996-2011 (Figure 3.15A) and these changes were pronounced in wards with high prevalence rates (3,5 and 15) (Figure 3.13C). In general, access to electricity increased from 1996-2001, but has decreased from 2001-2011 (Figure 3.15B).

3.7 Impact of MJD and beliefs about causation

There was a significant association between age and perceived cause of disease ($p=0.03$) as only individuals above the age of 60 believed MJD was caused by witchcraft, while younger patients most commonly cited soil, labour practices and food sources as the main causes. The greatest concerns reported by MJD patients were the loss of self-reliance (11/37), loss of livelihood (13/37) and the chronic pain and immobility (11/37). These themes were investigated further using data obtained from interviews (reported below).

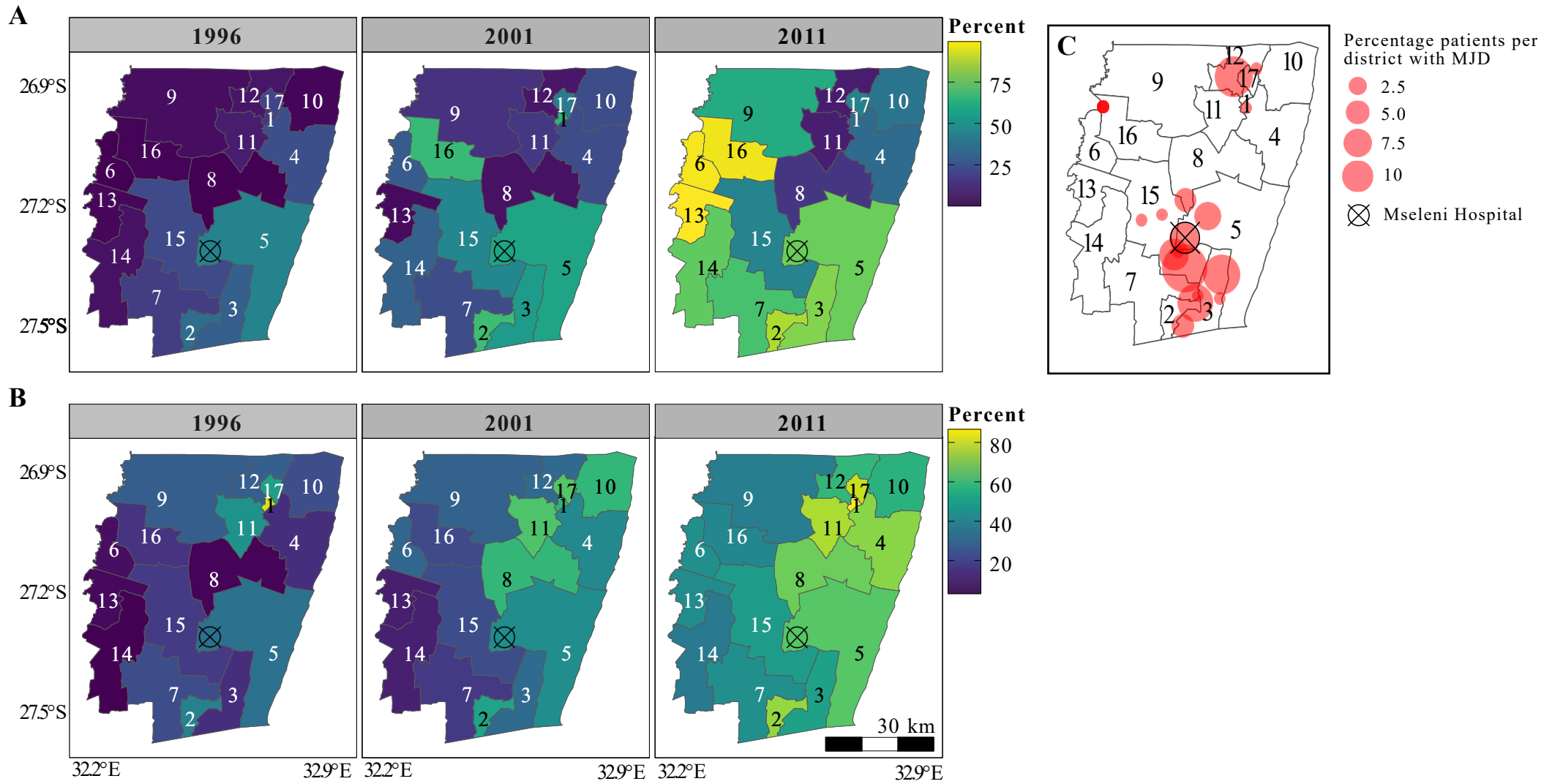


Figure 3.14 Geographic distribution of piped water (A) and formal dwellings (B) in Umhlabuyalingana from census data (1996-2011), MJD obtained from medical records (C) Crude prevalence frequencies calculated in the medical record review plotted relative to global positioning system (GPS) co-ordinates of patient-reported addresses.

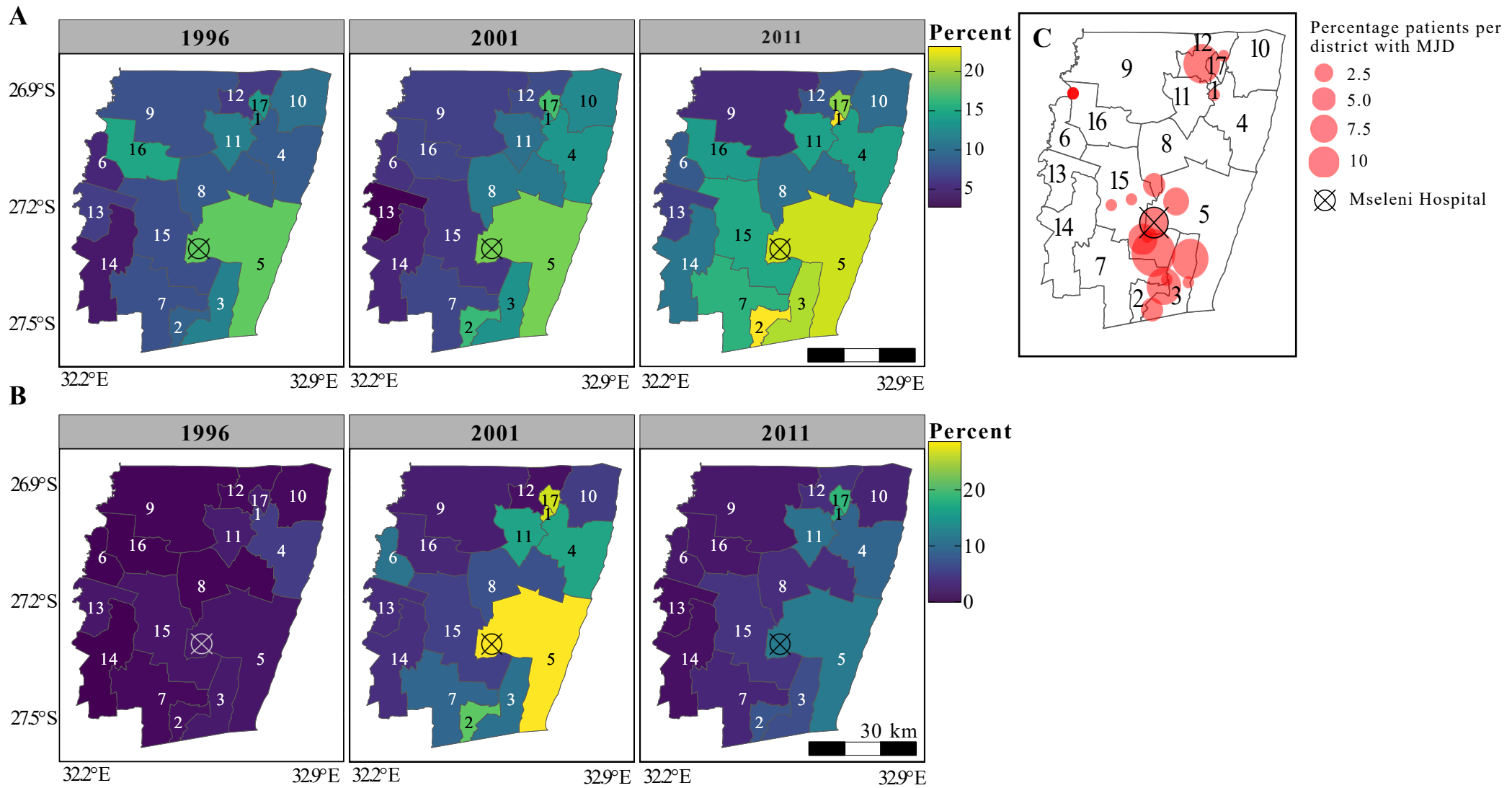


Figure 3.15 Geographic distribution of employment (A) and access to electricity (B) in Umhlabuyalingana from census data (1996-2011), (C) Crude prevalence frequencies calculated in the medical record review plotted relative to global positioning system (GPS) co-ordinates of patient-reported addresses.

3.8 Qualitative codes and themes

Over 10 hours of interviews with MJD patients, nurses and doctors were analysed. All patients had only lived in the uMkhanyakude region, with one exception being a patient who worked in Johannesburg for several years as a young adult. All interviewed patients had been treated for MJD at the Mseleni Hospital for more than 5 years. All doctors and nurses in the sample had experience caring for MJD patients at the OPD of the Mseleni Hospital. Nurses had more years of experience (10-30 years) at the Mseleni Hospital than several of the interviewed the doctors. Specifically, seven doctors had only worked at the Mseleni hospital for a year prior to interviews, while one doctor worked at the hospital for seven years and another for 29 years. Most of the nurses (5/7) were born and raised in Umhlabuyalingana (the region affected by MJD), while only 2/9 doctors were born and raised in this region. Interviewed nurses mostly trained at the Mseleni Nursing School (closely affiliated with the Mseleni Hospital), while doctors mostly trained internationally at universities in Europe or Africa. All patients and nurses, and two doctors reported Zulu as their first language.

While both men and women experienced pain and functional limitations, the experience and description of these differed greatly and will be explored below. Findings from thematic analyses of interviews are reported according to categories in Kleinman's explanatory models of illness (1978): (1) onset of symptoms, (2) aetiology, (3) pathophysiology, (4) course of illness and (5) treatment. While aetiology is usually presented first in this model, the onset of symptoms is critical to establish the context for the other variables.

3.8.1 Onset of symptoms

Patients had difficulty recalling year of onset or diagnosis, and described onset relative to the incidence of significant life events (such as the having children, car accidents, and moving residences) or a specific year (Table D8):

"I was involved in car accident in 1999...So as time went by, when I was back here in Mseleni... So that's how the issue started because the leg that I injured is the one that I ended up having an operation on."

"A long time... years. Because when I had children, it had already started feeling sore."

Two doctors stationed in the maternity ward noted that MJD was unlikely to be linked to childbirth, with one doctor noting the lack of joint pain in the younger group of mothers (Table D8):

"Certainly, they're not complaining of the symptoms. Um, suggestive of MJD. But they are a younger population. I mean, there's most of our women [in maternity ward] would be under forty, so you would find the younger population wouldn't be complaining as much."

Another doctor believed the joint pain symptoms treated at the Mseleni Hospital was likely associated with obesity and not MJD, stating:

“I do find that mostly the [early onset] joint pain is in obese patients. So, it's difficult to distinguish between whether it's an early type of MJD over whether it's actually just extra weight on the joints.”

Nurses and doctors believed the onset of MJD was associated with aging (Table D8). The bilateral onset of hip pain and disability in patients younger than 50 years old was cited unique to MJD:

“In, in my community, seventy is expected to be older, but here in this community fifty-five, sixties they come for operations here.”

Three doctors with more than 5 years of experience at the Mseleni Hospital described MJD as a generational disease that affected a progressively aging cohort. These doctors reported an older onset age and less severe onset in their patients (Table D8):

“But now I think we haven't really had a lot of new diagnoses. So, I think the, the group that we still have are more the advanced ages and it's mostly that generation that is progressively getting older. Um, and then I think, I think we have less young patients now with MJD.”
– Doctor

“We're just dealing with a cohort now that are aging. Some, some, some who had the disease 40 years ago. It's the end, the tail end of the disease... Maybe, we're not going to see twenty-year-olds with the disease, much in the future.”
– Doctor

“I was seeing people at that age group – twenty-five, twenty, twenty-five, thirty years old with, with Mseleni joint disease. Quite severe to the level of not being able to walk without sticks”
– Doctor

3.8.2 Aetiology

Patients generally invoked spiritual, social and environmental theories surrounding the aetiology of MJD, which contrasted to the environmental and social theories invoked by doctors (Table 3.10). Nurses represented an intersection between these two groups, invoking spiritual, environmental and social theories of causation. Natural causes were described by 13 participants, with 34 references made to natural causes throughout the interview process (Table 3.10). Notably this belief about causation was conserved most between doctors, nurses and patients interviewed in this study.

“It started like that until they later said it's caused by the soil when they explain it. Because just like these ones [researchers]. I don't even know how many times they would come looking for the cause of this thing.”
– Patient

“It is the work we are doing, maybe. Also, it is long working hours. ... Hey, we are doing different work. We are working at the contracts; we are working at the hospital. We stand for a long time, maybe I might end up having MJD. Maybe, I'm not sure?”
– Nurse

“I would think maybe it's related to what people eat, you know they plant, plough, eat. Or the type of water that people drink... The type of water that we drink, it could have those minerals...” – Doctor

Over half of the patients (4/6) believed MJD was caused by the soil in the affected area, stating that this was a common belief in locals, healthcare providers and researchers (Appendix D8). A similar sentiment was shared by 5/7 nurses, who maintained both doctors and patients believed the cause of MJD was soil.

“Ei! I haven't heard anything apart from the fact that it's the soil where we live.” – Patient

“They [the community] say it's caused by the sand but now there is sand everywhere... So that's why I don't believe in that theory. There's a lot of sand in Manaba compared to here but they are still saying it's the sand. I don't believe in that”. – Patient

“I'm not sure, but what I heard before... it was the, the soil on the geographical area. That's what we heard. Though, it was also not clear which way... It's what the community says and what the doctors think.” – Nurse

Table 3.9 Explanatory models of Mseleni Joint Disease (MJD) from interviews with MJD patients, nurses and doctors.

| | Patients (n) | Doctors (n) | Nurses (n) | Total participants (n) | Total references (n) |
|--------------------------|-------------------------|------------------------|-----------------------|---------------------------------------|-------------------------------------|
| Supernatural | 1 | 1 | 1 | 3 | 3 |
| Natural | | | | 19 | 42 |
| Environmental | 5 | 4 | 4 | 9 | 16 |
| Biological/Physiological | - | 6 | 5 | 11 | 21 |
| Lifestyle | - | 2 | 3 | 5 | 7 |

Explanatory models were generated from interview responses. Excerpts from interviews in Appendix D

Other environmental causes cited were locally grown crops, leading to the suggestion of the soil being a cause due to contaminants or nutrient deficiencies. Doctors and nurses spoke more confidently about their hypotheses about causes of MJD, and sometimes they explained their beliefs surrounding causation by describing biological mechanisms linked to these (Table D9). Soil as cause was described as a result of joint stress and strain due to lifestyle practices or toxin exposure due to consumption of locally grown foods or mineral deficiencies in the soil.

“...And they were travelling from the young to older age. Without using a car. Walking 10 to 12 kilometres, carrying water on the head. Doing everything using their foot.” – Nurse

“I don't know. They, they research, but they say it's this soil, it's not having the iron.” – Nurse

“What about the food that is growing in the soil? Is the soil setting a problem with the food that we are eating? Because maybe there are toxic things that are already in the food.” – Doctors

Several nurses and patients believed that it was common knowledge to researchers and the community that MJD was caused by soil (Table D9). One theme that was apparent was nurses believed the physical labour linked to ploughing, walking far distances and collecting water were aetiological of MJD (Table D9). The water source and food sources were also cited as aetiological by several doctors who suggested a link between the reduction of subsistence farming and MJD prevalence in the region.

“But, most likely cause most people now don't plough, people don't have their own gardens, private gardens and everything, so they buy from shops to eat. Most food does not come from here, so I will lean more towards the water, the type of water that we drink.” – Doctor

“It might be that, um, that their nutritional deficiencies that they had then, which are not here now because we have a much different diet...” – Doctor

“And so even if they out of work they don't very seldom even garden. If they've been to school, somehow schooling seems to tell them that agriculture is not for them.” – Doctor

All patients reported access to household taps in their homes or on their property, prior to this, patients relied on water collected from nearby rivers (Mkawini and Sibhayi) or access points (community wells). No association between past or present water sources and MJD were identified. All patients reported past daily water collection in buckets and drums carried by head or hand. Several patients noted the impact of droughts in the region on nearby water sources causing them to travel further distances to collect water.

Patients were aware of community-wide beliefs about the spiritual causes of MJD (Table D11). Only one patient cited this belief as their own, believing that MJD was caused by someone in the community cursing them, using *umeqo*. The belief held by patients that MJD is caused by displeasing ancestors was described by nurses and doctors only. Doctors and nurses provided information on TAM beliefs surrounding *umeqo*. Several doctors stated that patient-held beliefs of the aetiology of MJD pointed to psychosocial tensions within families and the broader community (Table D15).

“In this community, there is a belief that there is a condition called umeqo. So umeqo is, um, when a witch basically, casts a spell on a path that you're gonna' walk on and as soon as you step over that spell then you may have issues with your legs and mobilization. And. So it's likely that as the MJD develops, that can be viewed as some form of um, witchcraft or sorts.” – Doctor

“... but other people out there may not necessarily understand the pain that you are in, because you probably don't have a wound or you didn't have an accident. So, they don't accept the fact that you are disabled by the condition [MJD] that's going on.” – Doctor

Interestingly, doctors and nurses cited multiple causes while patients largely cited singular factors drawing contrast between biomedical perspectives of causation being multifactorial versus traditional beliefs of singular causes for conditions (Table D 9-11).

3.8.3 Pathophysiology

Only nurses and doctors spoke about the pathophysiology of MJD, with sole emphasis on joint inflammation and cartilage erosion (Table D12). The mechanism of MJD was commonly described by nurses referencing soil as the aetiology.

“It’s that swelling... um, they think there is the bad blood that has accumulated there. So when they cut it a little bit to make those caba marks, that blood, that bad blood will come out.”
– Nurse

“...it’s the sand that they are walking on that causes the corrosion of bone and the... And this of the cartilage?”
– Nurse

“Although it’s not an inflammatory arthritis, you know once you’ve got wear-and-tear it creates inflammation.”
– Doctor

3.8.4 Course of disease and impact

All interviewed patients reported chronic pain and immobility in affected joints necessitating the use of walking aids such as crutches, walking sticks or walking frames (Table D13). Experiences of pathology bilateral hip pain and pathology dominated the discourse on the course of disease in patients, nurses and doctors. Doctors described a characteristic gait adopted in MJD patients due to joint degeneration and stiffness in the absence of physiotherapy with time.

“The pain ... is on my hip, the one on the left. But also, then again when it’s going to rain or the weather conditions have changed or will change”.
– Patient

“I just both, it’s, it’s pain on when they’re moving like this [gestures a shuffling movement] when they walking on the joints, the stiffness of joints.”
– Nurse

“...they’ll usually walk with a limp, but it’s not a usual limp that they walk in, it’s sort of a swaying gait from side-to-side.”
– Doctor

“I think one of the one of the big things that we used to see was, was severe joint constrictions. Where you had flexion deformities or windswept deformities without any having had any physiotherapy.”
– Doctor

3.8.4.1 Impact of MJD in the community

MJD impacted the psychosocial and economic conditions of MJD patients and families (Figure 3.16). Loss of financial and physical independence and self-reliance was cited as the greatest concern of all surveyed patients (Figure 3.16; Table D15). Care-provision was largely gendered, as daughters or daughters-in-law (*makotis*) were the primary carers of MJD patients.

“I don’t except this for my own child. She’s someone’s child [daughter-in-law], what I mean to say is he has a child with my child [daughter-in-law]. She helps me, but before she was here I used to struggle for myself.” – Patient

“My son’s wife goes [to collect water]. How could I do it since I walk like this?” – Patient

Doctors and nurses noted that MJD sometimes resulted in stigmatisation when patients were unable to partake in household activities or fulfil social roles due to pain and disability (Figure 3.16). Younger patients got little support for MJD from their families. Furthermore, one nurse noted the stiffness in the hip joints impacted sexual intimacy in some patients.

“I think the immobility part becomes sort of the point of stigmatization. For instance, I remember someone in the community had two wives, one of the wives didn't have MJD and then the other had MJD. So it was almost like this one [with MJD] was the lazy one, just because she couldn't mobilize.” – Doctor

“So if it is a younger population, you may find that they're not, uh, sympathetic towards those women that are having the condition. Whereas you kind of look to older people with the joint disease and you're kind of saying, well the gogos' [grandmothers/older ladies] are sitting at home and they're being cared for, but they're not expected to do a huge amount. But if you are like the daughter-in-law, you're expected to carry your weight, you're expected to do the work.” – Doctor

“Cause the hip used to be stiff. The, the hip or the, the knees. So, then they would be unable to open [during sex].” – Patient

Nurses stated that patients that lacked family support received some care from neighbours, but that they were generally worse off (Table D15). The socioeconomic impact included early retirement, lack of employment and limited education in young women taking care of MJD-affected relatives (Figure 3.16 and Table D16).

3.8.5 Treatment

Doctors, especially those new to the Mseleni Hospital had little confidence in their ability to diagnose MJD. In general, doctors described identifying MJD by taking a history, conducting clinical examinations, serological tests and radiographs to exclude other conditions that may be causing the patients symptoms (Table D17). The uncertainty associated with diagnosing MJD patients lay with making a differential diagnosis of MJD relative to generalised OA.

“What sort of diagnostic protocols do you use to identify MJD in patients? Is there a standardised protocol? As far as I'm aware, there's not”. – Doctor

“... rule out of other known pathologies. So if you can see they've got TB. If you can see they've got gout. If you can see they got rheumatoid. Or, they've got a congenital abnormality of the bones. Then you would rule them out of being MJD.” – Doctor

“But a patient to me who comes with either, elbow, shoulder, knee, ankle joint-related problems. I approach them the same way. Unless I can maybe getting some advice to say, this

one we can classify as MJD.”

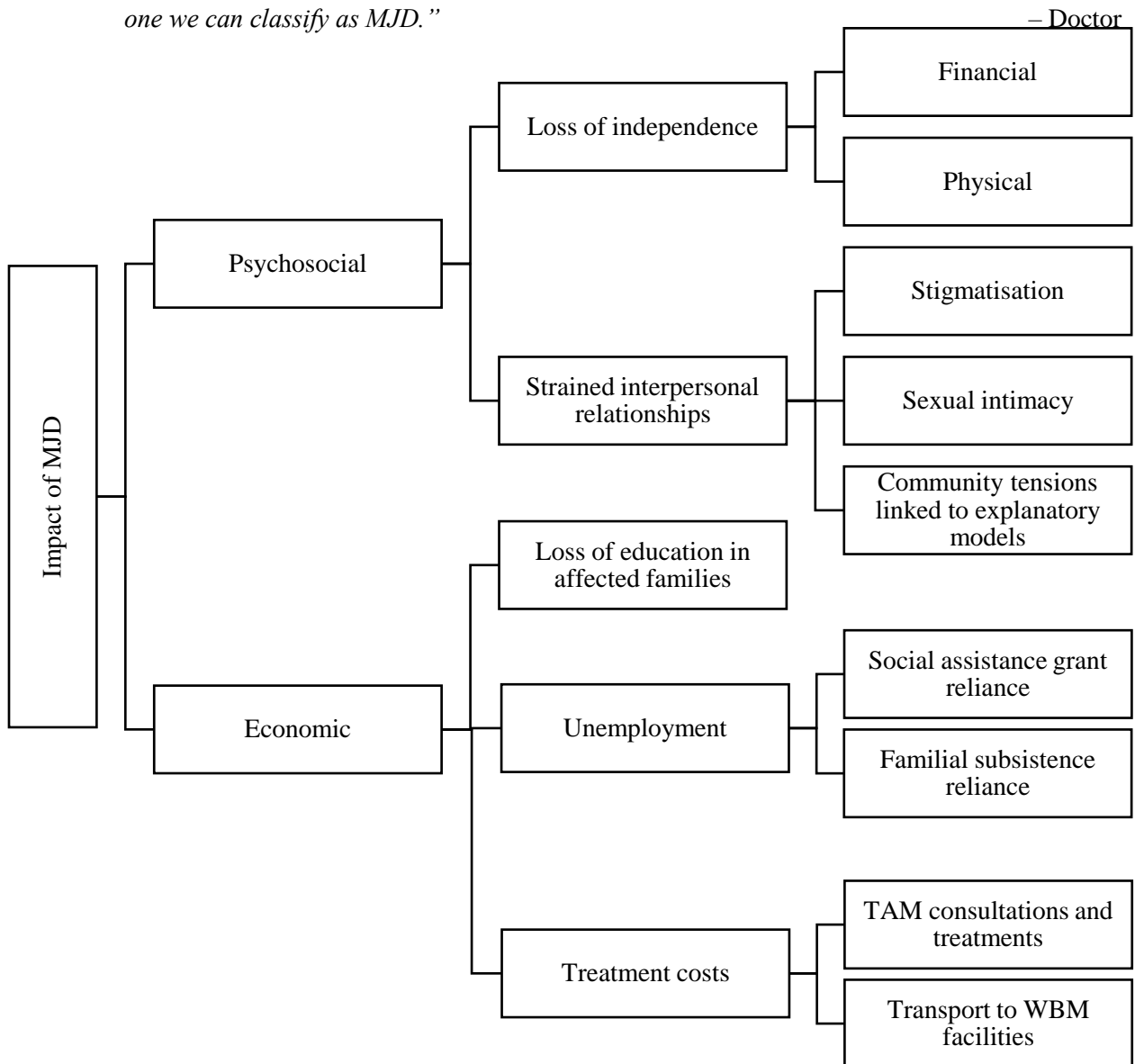


Figure 3.16 Thematic framework of psychosocial and economic impact of Mseleni Joint Disease (MJD) developed from interviews with MJD patients, doctors and nurses.

Doctors report using pain management and cortisone injections into the joints to manage pain and maintain mobility in affected joints. Patients discussed using medicines prescribed by doctors at the Mseleni hospital to manage pain, referring to these by colour. Several doctors cited concerns that patients with chronic pain try unknown pharmaceutical drugs that are sold irregularly in the community (Table D18). This was described as a limitation treating patients effectively because interactions between prescribed medicines and the unknown pharmaceuticals could not be managed.

“Here they just give us these ones. We call them amodolo, they’re greenish on one side and yellowish on the other.”

– Patient

“Although it's not an inflammatory arthritis, you know once you've got wear-and-tear it creates inflammation. Particularly joints like the knee, which is a fairly unsupported joint. It gets it [steroidal injection]. It certainly does give a pain relief and improvement; patients certainly appreciate it.”

– Doctor

“Ah, they've also tried medicines that are just sold by anybody, at pension pay-outs. There are lots of people touting yellow pills and red pills and blue pills. Pharmaceuticals that are being sold irregularly by people with no knowledge of their safety and risk.”

– Doctor

The absence of a standardised treatment protocol was cited as a limitation to patient outcomes as not all doctors prescribed physiotherapy or lifestyle interventions to patients to maintain joint mobility (Figure 3.17). Some patients felt that physiotherapy helped mobility, while others stopped these treatments as they did not feel they were helping. Patients reported good outcomes from surgical interventions but were reluctant to undergo further procedures due to fear (Table D18).

“The doctors gave me these booklets to see what exercises I can do. So I do what they said I should do”

– Patient

“I stopped going because it felt like they were just finishing me off when they were doing it.”

– Patient

“I only knew pain that was different, and which was slightly better after surgery. But I felt a difference because when I came back after the first surgery, I found out where my hip bones lie, they really opened me up it's scary.”

– Patient

Doctors from the orthopaedics unit reported difficulties conducting joint arthroplasties in MJD patients due to unique joint shapes and advanced destruction, with one stating:

“It can be more difficult because partly because the joints are generally more advanced destruction, and the joint structure is often a lot smaller. So, the people tend to be fairly small and then they have quite deformed joints.”

Doctors and nurses believed that the Orthopaedics Unit at the Mseleni Hospital provided effective treatment once patients were diagnosed, but they requested more support in the diagnosis and referral process. Doctors desired more training on MJD and *pro forma* for diagnosis and treatment was suggested (Figure 3.17). Sociocultural barriers to treatment listed by doctors included communication barriers due to age, gender, linguistic and cultural differences between MJD patients and healthcare providers (Figure 3.17). Community held feelings of mistrust and socioeconomic conditions limited care-seeking and access to healthcare in MJD patients (Table D17-D18). While almost all participants believed management of MJD could be improved, the doctors felt MJD patients were being well managed, and the patients appeared to echo this sentiment. Patients spoke positively about the continuity of care and the communication with their doctors (Table D17-18).

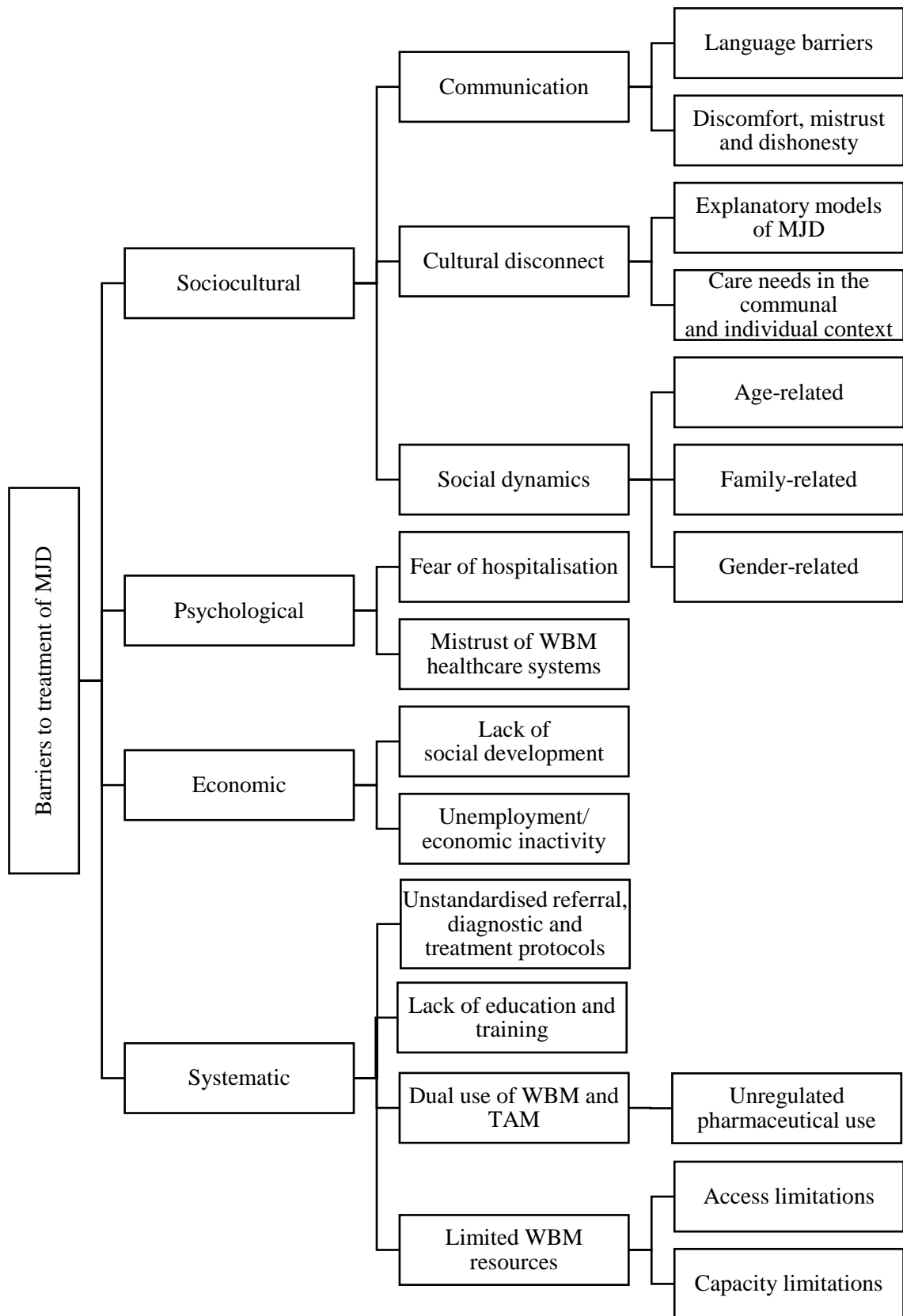


Figure 3.17 Thematic framework of the sociocultural, psychological, economic and systematic barriers to the treatment of Mseleni Joint Disease (MJD) from interviews with MJD patients, doctors and nurses.

In general, doctors described TAM as unscientific, and harmful. The lack of regulation or standardisation of TAM was cited as a reason these systems could not exist in the national healthcare system in SA. Some doctors expressed willingness to use traditional medicines if they were well researched and understood but expressed concern that this may give healing practices further credibility in the community (Table D18). Several patients denied using TAM to treat MJD, despite the presence of caba marks, and various traditional goatshair bracelets during interviews. One patient who discussed using TAM to treat MJD prior to WBM, described a treatment called *caba* (making cuts to painful joints and applying traditional medicines called *muthi*), and this was also discussed by the survey nurses.

“It [MJD] has affected me because when you’re felling a constant pain even if you take medication... So, we started with the traditional route, do you see these cuts, they did this saying that they were healing us saying that it will end but it never stopped. I only knew pain that was different, and which was slightly better after surgery. Because it’s like the blood they removed from this region they operated... I don’t know. But, I felt a difference because when I came back after the first surgery.”
–Patient

“Yeah, and when that, is that swelling. Um, they think there is the bad blood that has accumulated there. So when they cut it a little bit to make those caba marks, that blood that bad blood will come out.”
– Nurse

3.8.6 Impact of COVID-19

To reduce burden on healthcare system, the National Healthcare system prohibited elective procedures during the COVID-19 lockdown period in South Africa. One doctor mentioned postponing several surgeries, but that patients were monitored continually and followed up during this period, *“the ones that were planned for surgery were still given dates to come in for monitoring and see how bad, are they getting worse?”* (Table D20). While patients were still being cared for chronically, the MJD clinic had stopped running in 2020 due to COVID-19. One doctor said when asked how treatment of MJD could be improved, *“Um and I suppose having a specific targeted clinic for them, which we’ve kind of lost throughout this year”*. Only 1/6 patients interviewed mentioned not going to hospital due to fear of COVID-19.

3.9 Results summary

From medical records aging and female gender were identified as risk factors of MJD, however, aging was a confounder of the association between gender and MJD, as the sample was skewed in the representation of elderly women. No cases of MJD were identified in patients below the age of 35 years old in the medical record review. MJD patients were residents to areas in close vicinity to the Mseleni

Hospital, which were also adjacent to public transport routes and rivers, but with limited access to piped water. MJD was prevalent in families, and affected relatives were more likely to be women than men. Results from the meta-analysis suggested a declining prevalence of MJD from 28% (1973) – 9% (2019), corresponding to a temporal decrease in the likelihood of MJD in women and younger patients. From surveys of MJD patients, it was evident that difficulty recalling onset of MJD was associated with longer disease durations. The onset of MJD occurred most frequently as unilateral pain in the hip and knee joints which inevitably progressed to bilateral pathology. Lumbar pathology was only detected in MJD patients with disease durations of more than 5 years. No significant co-morbidities were associated with MJD, and no records of protrusio acetabuli or MED were found in medical records of MJD patients. No standardised diagnostic or treatment protocols were identified in medical records. Patients were more likely to adhere to pain management using NSAIDs than physiotherapy or surgical interventions. MJD was significantly associated with subsistence farming and poor access to public transport at least ten years prior to this study. Patients largely reported transition from a subsistence-based farming income to a monetary-based income, largely linked to social assistance through pension grants. This agreed with significant improvements in access to piped water, formal dwellings, employment identified in census data in the MJD-affected region.

In general, qualitative findings from interviews agreed with quantitative results. Explanatory models of MJD were supernatural (witchcraft or ancestral displeasure); natural (nutritional deficiencies, ‘genetics’ and/or environmental); and/or social (gender-based practices and lifestyle). Interestingly, doctors and nurses cited multiple causes while patients largely cited singular causes of MJD. The psychosocial impact of MJD included loss of independence, strained interpersonal relationships and stigmatisation due to an inability to fulfil social expectations. Patients discussed problem-focussed coping strategies and dependence on family and neighbours for care-provision. The economic impact of MJD included loss of education, unemployment and financial pressure due to treatment costs. Doctors described the uncertainty associated with diagnosing MJD and treating MJD, and suggested improvement through standardised protocols and MJD-specific training. Poor adherence to physiotherapy and lifestyle interventions in patients was evident. Barriers to MJD treatments were primarily psychological, sociocultural, economic and systemic. Patients were reluctant to discuss their use of TAM to treat MJD, while doctors and nurses openly discussed patients use of both TAM and WBM to treat this condition. Several patients reported using TAM prior to WBM to treat MJD.

Chapter 4: Discussion

At the outset of this thesis, MJD was as described as a bilateral endemic osteoarthropathy of unknown aetiology (Wittman & Fellingham, 1970; Agarwal *et al.*, 1997; Gibbon *et al.*, 2010). Effective management and treatment of MJD has been limited by a poor understanding of the risk factors linked to MJD (Mann & Fredlund 1988; Fredlund, 2003; Gibbon *et al.*, 2010) and the socio-cultural contexts shaping experiences, perceptions and treatment-seeking approaches of affected individuals. A mixed methods study was conducted to explore biomedical and sociocultural aspects of the MJD phenomena using a biocultural approach. This is the first mixed methods research on MJD, and this work was inspired by a review by Gibbon *et al.* (2010) that cited cogent evidence in favour of a multifactorial aetiology of MJD. The aims of this study were (1) to identify biological, spatial and sociocultural risk factors associated with MJD and (2) to examine explanatory models of MJD and treatment seeking behaviours held by MJD patients, nurses and doctors at the Mseleni Hospital. Quantitative and qualitative analyses were used to explore different biological, environmental and cultural factors associated with MJD. By using a pragmatist framework and the biocultural approach, empirical and descriptive precision were combined in a single study to provide a multi-level discourse on MJD, including voices of those this research impacts: patients, community members, doctors and nurses. This chapter provides a discussion of the main findings pertaining to risk factors, explanatory models and treatment seeking behaviours associated with MJD. The delicate relationship between TAM and WBM in treating MJD will be discussed and recommendations for improving the management and treatment of MJD at the Mseleni Hospital will be made.

4.1 Risk factors of MJD

This study started by asking a seemingly simple question: what causes MJD? The first step towards assessing risk factors of MJD was a hospital-based medical record review to explore the demographic and geographic distribution and prevalence of MJD. Medical records provide a cross-sectional ‘snapshot’ of disease distributions and are revered for their ability to provide insight into longitudinal patterns of diseases and their treatments over a series of visits (Bagley & Altman, 2016). Despite these benefits, this resource measures risk factors and disease outcomes at the same time, and therefore lacks the temporality needed to determine whether putative causes preceded the development of diseases. Furthermore, medical records are not necessarily representative of the underlying healthy population in a region (or the entire population-at-risk) as this sample exclusively comprises those seeking care for an illness at a healthcare facility. As such, the prevalence calculated from hospital records in this study approximates the burden of MJD on the Mseleni hospital and not necessarily the prevalence of MJD in entire affected region. Despite these limitations, however, our study found that trends in prevalence and demographics from medical records closely resembled those from other population-based surveys.

MJD was estimated to have a point prevalence of 9% in SABP adults from the uMkhanyakude region that were availing care at the Mseleni hospital during the sampling period. This study provided the first prevalence estimate of MJD since a population-based survey in 1973, 1974 and 1985 (Fellingham *et al.*, 1973; Lockitch 1974; Yach & Botha, 1985) and a hospital-based survey in 1987 (McLaren *et al.*, 1987). There was a notable decline in prevalence estimates in the first three population-based surveys from 28% (1973), to 11% (1974) to 5% (1985). Findings by McLaren *et al.* (1987) were outliers to trends in prevalence results (2%). This is likely because McLaren *et al.* diagnosed MJD in all patients with unilateral or bilateral hip pathology, and their sample may have included of patients with other joint diseases like generalised OA. While differences in results between studies included in the meta-analysis and our medical record review may be because our study estimated prevalence using medical records, the concordant patterns in demographic distributions and prevalence rates suggests a degree of robusticity in our findings.

One of the strengths of our medical record review was that MJD diagnoses were confirmed from X-ray findings recorded in medical records. Previous population-based surveys sampled MJD in Kraals or homesteads, which was costly, logistically complex and timeous to organise (Yach & Botha, 1985). As a result, these studies relied on researchers (doctors, nurses and scientists) to diagnose MJD based on participant-reported symptoms and in some cases, proxy reporting of symptoms from neighbours or family members when individuals were absent from kraals (homesteads) during sampling (Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985; McLaren *et al.*, 1987). McLaren *et al.* (1987) reported proxy reporting of MJD in 52% of participants because vast distances, rough terrain and limited access to telephones prevented follow up in patients who were absent during sampling. MJD was more common among those interviewed (13% of males, 20% of women), than those assessed through proxy-reporting (3% of males, 6% of women) (McLaren *et al.*, 1987). This could be because MJD-affected patients were more likely to be at home during sampling due to immobility and/or because respondents were unaware or had forgotten about MJD in those absent from home. While our use of medical records to confirm diagnoses mitigated against errors linked to proxy-sampling, our sample was less likely to include patients with severe physical or financial factors constraining access to the Mseleni Hospital. Despite differences in the study design, sample size and sample selection in our study, our findings provide an essential update on the point prevalence of MJD and indicate a significant burden of this disease on the OPD of the Mseleni Hospital.

When surveyed patients were asked about the history of MJD in their families, it was evident that in several cases patients were unaware of their family histories of MJD. The prevalence of MJD on the maternal line was evident from patient surveys and requires further exploration. While no evidence of mendelian inheritance has been identified in MJD patients (Lockitch, 1974; Ballo, 1998), complex genetic mechanisms such as imprinting, epistasis and polygenic susceptibility may be operative in families and individuals affected by MJD.

4.1.1 Gender as a risk factor of MJD

Gender was significantly associated with MJD, and women were nearly twice as likely to have MJD than men (OR= 1.88, $p=0.03$). Our findings were largely in agreement with studies included in the meta-analysis, which reported a higher likelihood of MJD in women than men (Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985; McLaren *et al.*, 1987). A decline in the likelihood of MJD was observed temporally from 1973 (OR=5.08, $p\leq 0.0001$) to 2019 (OR= 1.89, $p=0.04$), with results from McLaren *et al.*, (1987) the exception due to sample size disparities in the number of men to women in the sample (OR=6.76, $p\leq 0.0001$). Lockitch (1974) found that men were also less likely to participate in surveys as they reportedly believed participation may result in hospitalisation. The fact that fewer men than women were sampled in the medical record review in our study, suggests gender-linked differences care-seeking at the Mseleni Hospital.

While the higher prevalence of MJD detected in men than women may be linked to sampling disparities, it may be suggestive of gender-based differences in exposure to risk factors of MJD. *et al et alet al* Fellingham *et al.* (1973); Lockitch *et al.* (1973b) and Yach & Botha (1985) reported that men were largely absent from the region during sampling due to circular migration in response to employment opportunities in more developed regions. This has led to the suggestion that the lower prevalence in men indicates that circular migrants do not experience the same magnitude or duration of exposure to disease determinants due to their prolonged absence from the area (Lockitch *et al.*, 1973b; Yach & Botha, 1985). The higher incidence of OA and other degenerative joint conditions in women throughout the world, however, may suggest a biological or genetic predisposition to joint degeneration (Woolf & Pfleger, 2003; Litwic *et al.*, 2013).

Our study found that age confounded the association between MJD and gender, suggesting that age-linked differences between men and women may be contributing to MJD. The incidence of knee, hip and hand OA is known to be higher in women and the prevalence is shown to increase rapidly around the time of menopause (Srikanth *et al.*, 2005). As MJD was most prevalent in elderly women, hormonal changes linked to aging may be causative of this condition. While Cirillo *et al.* (2006) reported low oestrogen levels to be protective against hip OA, this was later refuted by de Klerk *et al.* (2009) who conducted a meta-analysis and reported clear association between low oestrogen and hand, knee or hip OA in women. The link between oestrogen in aging women and MJD is yet to be assessed, and further work is needed to clinical research is needed to explore the interplay between various hormones and joint degeneration in both men and women with MJD.

Another explanation for the higher prevalence of MJD in women may be gender-based division of household tasks as women in the MJD-affected area traditionally retain 'domestic' roles and responsibilities, which include collecting water, caring for children and ensuring there is food for household consumption through crop cultivation or shopping (Lubbe, 1973; Hazell, 2010). When

domestic responsibilities are fulfilled, women are involved in other kinds of work, which support household livelihoods and generate personal incomes (Fredlund, 2003; Hazell, 2010). Men's responsibilities are seen as 'productive' and include financially supporting the household, raising livestock, agriculture and when necessary, men fulfil domestic roles (Hazell, 2010). Differences in the distribution of MJD between men and women may be attributable to increased loadbearing activities in women and discrepancies in environmental exposures, both occurring as a result of cultural labour allocations (Lockitch, 1974). Labour intensive subsistence activities are performed by women in this community such as ploughing fields, herding cattle, and collecting water from lakes, boreholes and communal taps (Mann & Fredlund, 1988). The association between MJD with gender and subsistence farming and poor access to transport reported by surveyed participants may suggest a link between local lifeways and MJD.

Women and children can walk more than 10km to reach water sources, returning with water-laden buckets or barrels carried by hand or balanced on their heads (Lubbe, 1973; Mann & Fredlund, 1988). This repetitive action strains weightbearing joints like the knees, hips, spine, wrists, elbows and shoulders and may be linked to the onset of MJD. A cross-sectional study conducted in South Africa, Ghana and Vietnam, found that carrying water by head loading was associated with a two-fold increase in pain and joint degeneration in the spinal region compared to the pelvis (Geere *et al.*, 2018). While head loading of water from off-plot water sources seems unlikely to cause the characteristic hip pain associated with MJD it may contribute to secondary pathology noted in the lumbar spine of MJD patients. In interviews, woman noted receiving assistance from daughters-in-law, suggesting the cultural partitioning of labour continues despite changing sociocultural dynamics in the region. The domestic burden is particularly heavy for women from households that are poor or disadvantaged as technology, transport and money alter the social dynamics of access (Hazell, 2010).

4.1.2 Age as a risk factor of MJD

MJD was most prevalent in patients older than 70 years (23%), followed by 60-69 years (21%) and 50-59 years (18%), and no individuals with MJD below the age of 35 years were sampled. Our study identified no cases of MJD in individuals below the age of 35 years, and the average age of MJD patients was 65 years. Medical record reviews are known to over sample more elderly and unemployed individuals (Bagley & Altman, 2016), and thus, our sample was less likely to include young people with MJD or those with less severe pathology. It was evident from surveys that patients sought WBM care after experiencing limited ROM and chronic pain for several months and even years. Given this delay in treatment seeking – undetected, younger patients may be exploring other forms of healing outside of WBM. Ageing has been reported as the strongest risk factor for several degenerative joint diseases due to the reduction in regenerative capacity with age and accumulation of risk factors over an

individual's life course (Woolf & Pflieger, 2003). Therefore, the correlation between aging and MJD as seen in medical records, patient surveys and interviews suggests this causative relationship is unlikely to be due to sampling bias.

The trends detected in the meta-analysis suggested MJD was most prevalent in people over 50 years old, and the odds of MJD increased significantly with age from 1973 -2019. Once again, McLaren *et al.*, (1987) was an outlier to the overall temporal trends in the odds of MJD – likely due to differing sampling and diagnostic strategies discussed above. These results are suggestive of a change in the incidence rates of MJD. This also corresponds to suggestions by local doctors that MJD is a disease affecting an aging cohort, because risk factors associated with the disease have decreased with time. Nurse (1985) proposed MJD to be caused by exposure to a slow virus. While this provides a potential generational causative mechanism, no evidence in support of this has been found. The presence of a significant famine in the MJD-affected region in the 1920's may provide an explanation, causing poor growth and development in the parents of MJD patients who were children during this era (Lockitch, 1974). The familiar inheritance of MJD may be suggestive of an epigenetic transgenerational aetiology linked to undernourishment and famine conditions, as seen in survivors of the 1944-1945 Dutch famine (Veenendaal *et al.*, 2013). The absence of longitudinal data collection and sampling as seen in the Dutch famine study (Veenendaal *et al.*, 2013) makes identifying the origin of an epigenetic cause difficult. Whole genome sequencing and ribonucleic acid (RNA)-sequencing may help identify epigenetic aberrations in genes critical to cartilage, bone and synovium development and maintenance.

4.1.3 Geographic and socio-ecological risk factors of MJD

From medical records, it was evident that MJD patients were mostly from the Umhlabuyalingana 86% (57/66) municipal region, with 9% and 3% from the Big Five Hlabisa and Jozini municipalities, respectively. The highest prevalence rates occurred in the Ngutshane, Shihangawe, Manaba and Mseleni control areas (approximately 15%). The clustering of MJD around the Mseleni hospital may be because of the high density of residential settlements around the hospital (Yach & Botha, 1985; Gibbon *et al.*, 2010). Alternatively, it may point to a unique environmental aetiology around the sand forest belt in the region, as few cases have been detected in adjacent environmental zones (Yach & Botha, 1985). Thus far, MJD prevalence surveys haven't been localised around the Mseleni Hospital, and these results suggest the need for more studies to explore the prevalence in regions northwards of the hospital.

From the medical record review, MJD was detected most commonly in patients living nearer to major transport routes (concrete and tar roads). The detection of high prevalence rates around the Mseleni hospital is likely an indication of sampling bias as patients closer to this facility most frequently utilise the hospital. Due to limited access to transport and the immobility associated with MJD, patients

(including those with MJD) from more remote areas were less likely to be sampled. The absence of evidence of MJD in these areas suggests that the Mseleni Hospital sees few patients from these areas. Given the reliance on TAM in the region (Washington, 2010), it is likely that patients with severe disabilities that live further from WBM facilities may be using traditional medicines more than those with better access to the Mseleni Hospital.

The lower density of MJD patients adjacent to rivers, as assessed from medical records, may suggest that proximity to a primary water source could be a risk factor of MJD. It has been reported that those who live along rivers in uMkhanyakude region are less likely to walk far distances to collect water (Hazell, 2010). While the water source and mineral composition may be linked to MJD, this seems highly unlikely and has been investigated by Lubbe (1973). The association between MJD and water sources, may suggest that the proximity to rivers in the region is protective against the impact of loadbearing in the soft, sandy soil in the region. Thus, the clustering of MJD along the sand-forest zone (Pooley, 1996) may be due to the lack of water, the frequency of loadbearing linked to water collection and the further distances to water access points. The prevalence of MJD in the sand-forest zone is particularly interesting as several patients and nurses believed the sandy soil in the region to be causative of MJD.

Data from census publications and surveys suggested a change in the local economy from a largely subsistence-based to a monetary economy. Approximately 40% of MJD-affected individuals were receiving pension grants during sampling (corresponding to the age distribution of the sample), and 46% were employed during the survey period. MJD-affected patients cited an inability to do physical labour or grow their own food and believed that MJD had detrimentally affected their financial and physical independence. An extensive meta-analysis of patterns in arthropathies found that regardless of gender, arthritis was more prevalent among communities with historically limited social development (Brennan-Olsen *et al.*, 2017). Other endemic conditions of unknown aetiology such as Chronic Kidney Disease in Sri Lanka have experienced an increased prevalence associated social development, altered lifestyle practices and contaminated water sources (Liyange, 2019). Thus, the association between socio-economic changes and the decline in prevalence in MJD may suggest the aetiological role of poverty-linked access to resources and labour practices and MJD.

4.2 Onset of MJD

When surveyed and interviewed patients were asked to recall disease onset, there was no consensus when patients first experienced joint pain. Only 57% (21/37) of survey respondents described MJD-onset relative to the age or year that pain started, while 22% (8/37) described onset relative to life-stages (such as childhood, adolescence or adulthood). From surveys, it was evident that patients described onset occurring most frequently in adulthood (80%), with onset age ranging from 11-60 years and

peaking between 30-50 years. Similar results were observed by Lockitch (1974), where 13% of respondents noted MJD onset in adolescence or childhood compared to 68% of respondents reporting onset during adulthood, with the peak onset age being 40-60 years for men and 30-50 years for women. A statistical comparison of onset age between men and women was not possible in our study as only two men consented to participate in surveys. The two surveyed men reported onset in adulthood while women reported onset occurring between 17- 60 years of age, with a peak frequency being 30-40 years. The variable period/age of onset associated with MJD is concordant with findings in previous MJD surveys (Fellingham *et al.*, 1973; Lockitch, 1974; Yach & Botha, 1985) and the variability in onset age/period may be an artefact of the gradual and insidious initiation of pain and disability.

Onset in childhood and adolescence was reported by surveyed patients, but no evidence of hip or knee pain or other known MJD symptoms was found in the medical records of any patients under 35 years-of-age. While MJD was reported to have an early or precocious onset in children (Fellingham *et al.*, 1973; Lockitch, 1974), no evidence of this was found in medical records reviewed in our study. Yach & Botha (1985) reported a decrease in the incidence of MJD in adolescents and children and hypothesised a changing incident age. Findings from surveys suggest no association between patients' age and whether the onset occurred in adulthood, childhood or adolescence, indicating that regardless of age, the likelihood of developing MJD during adulthood was greater (83%). While the absence of joint pain in medical records of adolescents and children in our study may suggest a later onset, or that onset in subadults is rare, this trend is more likely due to the delayed reporting of pain as a symptom. Waller (1998) found that the mean duration of symptoms in MJD patients prior to diagnosis was 17 years, and that 89% of new arrivals to the MJD-clinic had X-Rays with ROME scores of 4, indicative of advanced joint destruction and immobility. The fact that MJD patients only seek care when this disease becomes incapacitating may be linked to limited access to healthcare, transport and lack of knowledge about how WBM treatments can help them. From interviews, it was evident that patients exhibited a mistrust for the healthcare system and uncertainty regarding the healthcare providers. Patients reported first attempting to treat MJD with TAM before WBM, providing another explanation for the WBM latent care-seeking noted in MJD patients.

Approximately, 19% of survey participants recalled MJD onset relative to a life event and the most commonly cited life events were childbirth (63%) and working in a different city (25%). The association between MJD onset and childbirth was suspected to be linked to biological, hormonal or physiological causes, but the fact that this association was not detected in the medical record review is evidence against the causative link between parturition and MJD. As patients described onset relative to the birth of a first, second and/or third child, this link may suggest that childbirth was used as an "anchor point" to remember symptoms and clinical events. "Anchor points" are temporal landmarks that people use when attempting to recall the relative occurrence of a health events (Barsky, 2002). Lockitch (1974) reported the use of childbirth as an anchor point, as several patients noted the onset of

joint pain after having children. Patients with MJD also had difficulty recalling symptom-onset and even their birthdates. Several studies have proposed using pre-defined anchor points from community or life events to facilitate recall of disease occurrences (Lockitch *et al.*, 1973b; Yach & Botha, 1985). The decision not to use anchor points in our study was taken to ensure that patient's recollection of MJD and their explanatory models were not influenced by using environmental, local or personal anchor points. Further work is needed to explore the onset recall process in MJD to maximise the information that can be obtained from the onset and rate of disease progression so this disease can be more effectively managed.

Interviewed patients recalled the earliest indication of MJD as swelling of the knees, pain and rapid tiring when walking. However, they only sought intervention for the pain when it impacted their ability to walk and perform daily chores. This phenomenon appears to be conserved in osteoarthritic conditions, for example, the lag between onset and treatment in Mexican and American patients was 6 years on average, with patients reporting care-seeking only when the pain diminished their quality of life (Amjadi-Begvand *et al.*, 2004). Similarly, patients in our study reported seeking care when the condition was advanced and resulted in disruptions to lifestyles. The more rapidly patients seek care, the less prone the onset date is to being underreported (Martorell *et al.*, 1976). Severe pain and depression are known to enhance recollection of symptom-onset in chronic pain patients (Miranda *et al.*, 2006), while longer periods between onset and recording are associated with poor onset recall (Martorell *et al.*, 1976). Evaluating onset of osteoarthritic conditions like MJD is notoriously difficult as patients are known to only seek care once the condition impedes their ability to perform normal tasks, which may be several months or years subsequent to onset (Amjadi-Begvand *et al.*, 2004; Ozgocmen *et al.*, 2009). A long-term study of at-risk patients (with a family history of MJD) is needed to determine when the onset of joint degeneration and pathology occurs, and how this correlates with patient-reported pain.

Inconsistencies were found between how MJD patients described the onset-dates to interviewers and how onset-dates were recorded in medical records by doctors at the Mseleni hospital. Doctors recorded symptom-onset dates in medical records for 31% of MJD patients, while interviewed and surveyed patients generally situated onset relative to anchor points as discussed above. For 11% of MJD patients identical onset and diagnosis dates (years or months) were recorded in medical records, for the remaining patients the median lag time between diagnosis and onset was 3 years, with a range of 1 month-54 years. These patients had extensive polyarticular pathology and immobility at onset, suggesting inconsistency in how onset was reported by patients and/or recorded by healthcare providers. As MJD is known to have a gradual onset (Solomon *et al.*, 1986; Agarwal *et al.*, 1997), it seems unlikely that the date of onset and diagnosis are identical given extent of bilateral hip and knee arthritis noted in the patients with identical onset and diagnosis dates. Instead, is it more probable that some doctors

recorded the onset and diagnosis interchangeably or that patients understood or reported these concepts interchangeably. The lack of standard recording in medical records is common when patients receive care from several doctors, who may take clinical history differently or ask different questions in each visit (Ozgoemen *et al.*, 2009; Bagley & Altman, 2016).

4.3 Pathology and disease progression of MJD

Our findings showed that the initiation of MJD occurred exclusively in the appendicular skeleton with secondary pathology in the axial region. Approximately 68% of surveyed patients reported onset of pain in the hip, followed by the knee (54%). Survey findings were consistent with results from medical records where the onset in the hip region was recorded for 73% of MJD patients, followed by the knee region in 45% of patients. The bilateral onset of MJD primarily in the hip joints followed by knees has been reported in previous radiological surveys (Lockitch, 1974; Solomon *et al.*, 1986). While our study found the onset of MJD was largely bilateral (52%) this was not statistically significant. Only 5% of survey respondents reported shoulder joint pain and 10% noted forearm (elbow joints) pain at onset, which increased significantly within 5 years from diagnosis to 15% and 30%, respectively. This was concordant with Lockitch (1974), who suggest pathology in the upper limbs (shoulders, elbows and wrist joints) was secondary to lower limb pathology and is largely found in MJD patients with bilateral joint immobility and disease durations of more than 5 years. It is important to note that our study relied on patient-reported pain, while medical records relied largely on data from clinical histories and radiographs. The absence of bilateral radiographs for each patient prevented us from confirming whether pathology exclusively occurred unilaterally or bilaterally. To an extent our findings are not in agreement with previous research which reported that MJD has primarily bilateral and uniform at onset (Lockitch *et al.*, 1973a; Solomon *et al.*, 1986; Agarwal *et al.*, 1997).

Our study exclusively identified lumbar spine pathology and pain in MJD patients with disease durations spanning more than five years. Radiographs from MJD patients with joint pain showed that MED was typically associated with morphological variations in the lumbar spine (Solomon *et al.*, 1986; McLaren *et al.*, 1987). Our study found no record of MED or protrusio acetabuli in medical records and we were unable to confirm this finding. Solomon and colleagues (1986) reported a higher incidence of pain and pathology in the lumbar region in MJD patients with more advanced MJD (bilaterally hip joint immobility). Given these findings, it is most plausible that MJD in the lumbar vertebrae is the consequence of biomechanical instability due to bilateral joint degeneration in the pelvic region. The shuffling gait adopted by patients with MJD is likely to place strain on the lumbar spine, therefore, pathology in the lower back may be a secondary symptom of MJD that is compounded further by variable degrees of lordosis present in the affected population. A pronounced lumbar lordosis is common in SABP and is usually asymptomatic, however, severe lordosis is associated with conditions

compromising the structural integrity of vertebrae (for example osteoporosis and spondylolisthesis) (Adebajo & Davis, 1994). No association was detected between lumbar pathology and gender in our study, and this was in contrast with findings by Lockitch (1974), where lumbar degeneration was identified more commonly in men than women. The disparity in our findings may be a consequence of a skew in our sample towards elderly individuals (average age of 65 years) and women. Lockitch (1974) reported that women with MJD were two times more likely to have pelvic pathology, while men were more likely to exhibit lumbar spine pathology. This led to the conclusion that lumbar pathology was linked to gender-linked differences in lifestyle and labour-practices (Lockitch, 1974). While our study found no evidence that spinal pathology was gender-linked, our results suggest that lumbar pathology could be linked to ‘wear and tear’ as a result of lifeways and aging.

No records of protrusio acetabuli or MED were found in medical records. This finding is particularly interesting as Solomon and colleagues (1986) proposed MJD comprises distinct subtypes associated with either protrusio acetabuli or MED, or a combination of both. According to those authors, each subtype has unique origins, disease trajectories, and therefore, differing management strategies would be required. This is not widely accepted due to the inconclusive clinical research on the significance of protrusio acetabuli or MED in MJD (Agarwal *et al.*, 1997). In our study, the absence of this information from medical records implies that doctors do not consider MED or PA significant in the daily management of MJD, and more information on these morphologies may be present in surgical records. A longitudinal survey of radiographs of MJD-affected and unaffected individuals was beyond the scope of this study, but a study of this nature is needed to elucidate the role of PA and MED in the pathogenesis of MJD.

No co-morbidities recorded in this study (for example, diabetes, cardiovascular disease, tuberculosis, malaria or HIV) were significantly associated with MJD. Furthermore, the onset of MJD was not linked to any systemic condition or disease. No brachydactylous dwarfism was observed in medical records and this may be due to poor record keeping or because the sample in the medical record review was not sufficient enough to detect brachydactylous dwarfism, which has a prevalence of 0.1 % in the population. Alternatively, the absence of brachydactylous dwarfism in medical records may suggest that this is not considered a co-morbidity that impacts the management of MJD. Further evidence that brachydactylous dwarfism is unlikely to be a significant co-morbidity in MJD patients was the agreement between the experiences of onset, course of disease and treatment in brachydactylous dwarfism-MJD patients and MJD patients of regular stature. A pathogenic relationship, if any, between brachydactylous dwarfism and MJD may have important implications for the aetiology, diagnosis and treatment of MJD.

Interviewed doctors noted prevalence of precocious joint pain in obese patients, however, they refuted MJD as the cause. Given this information, it is possible that young individuals with MJD are

being diagnosed with obesity-linked OA and are not being managed effectively. Obesity is known to increase the load on weight-bearing joints and is also suspected to increase joint susceptibility to damage through activation of inflammatory adipokines (Conde *et al.*, 2011). While obesity is a leading cause of joint degeneration in young people worldwide (Mork *et al.*, 2012; Glyn-Jones *et al.*, 2015; Usenbo *et al.*, 2015), little research has been done on the association between obesity and joint pain in young people in South Africa or the affected uMkhanyakude region. Obesity is known to significantly increase the risk of knee OA and accelerate its progression but has shown no clear association with hip OA (Mork *et al.*, 2012). As MJD primarily manifests as bilateral hip pain followed by bilateral knee pain (Lockitch, 1974), it seems unlikely that obesity is contributing to joint pain in MJD patients. It cannot be ruled out that young patients with MJD presenting to the Mseleni Hospital are being misdiagnosed due to obesity.

4.4 Diagnosis and treatment of MJD

No distinct diagnostic protocol for MJD was identified in medical records, and this was confirmed during interviews with doctors. The absence of serological tests or assessments of bone mineral deficiencies in medical records of MJD patients is reflective of the vastly under-resourced health-care systems in rural regions in South Africa. Additionally, the absence of inflammatory markers, rheumatoid factors or any significant markers of MJD in blood or urine precludes the use of molecular diagnoses (Changlong *et al.*, 1987; Sweet *et al.*, 1987). MJD is diagnostically approached similar to an OA: obtaining a clinical history of symptoms, assessing ROM, identifying joint pain and requesting X-rays (Lockitch *et al.*, 1973b; Du Toit, 1979; Solomon *et al.*, 1986). The lack of radiologists at the Mseleni hospitals requires that doctors interpret radiographs, and therefore the effectiveness of diagnosis from X-rays and pathology analyses relies on clinical experience. In the medical records, the most commonly recorded symptoms were limited range of movement (83%), radiating leg pain (59%) and swelling/redness around knee joints (15%). The presence of joint swelling/redness is surprising as these are characteristic of joint inflammation, however, MJD is a non-inflammatory arthritis (Nurse *et al.*, 1974; Changlong *et al.*, 1987). Localised inflammation has been detected in painful joints of MJD patients (Lockitch, 1974), but this does not mean that MJD is an inflammatory arthritis, as joint inflammation is a common symptom in patients with generalised OA (Malemud *et al.*, 2003; Palmer *et al.*, 2013; Glyn-Jones *et al.*, 2015). Inflammation identified in the knee joints of MJD patients probably shares the same cause of OA, which is the upregulation of inflammatory cytokines and macrophages in the synovium in response to mechanical activity (Tetlow *et al.*, 2001; Mueller & Tuan, 2011).

From surveys, we were able to estimate the delay to diagnosis from symptom development as 5-8 years. In OA, delay to diagnosis is common regardless of the age of symptom onset. Delays generally range from 5.6 years (Ozgoçmen *et al.*, 2009) to 15.3 years (Stone *et al.*, 2005). In conditions

with an onset in juveniles, like ankylosing spondylosis, there tends to be a longer delay in diagnosis of 15.3 ± 0.79 years in juveniles compared to delays of 7.6 ± 0.20 years in individuals who develop symptoms in adulthood (Stone *et al.*, 2005). In this study, recall bias was likely to lead to an underestimation of the true disease durations due to greater delays in diagnoses (Stone *et al.*, 2005; Gensler *et al.*, 2008). Reliable recording of onset and diagnosis is critical in determining disease duration and ensuring patients are treated optimally (Amjadi-Begvand *et al.*, 2004).

Disease duration is often specified according to the date of diagnosis (not onset), which can vary based on the assertiveness of the patient or the skills of the clinician seeing the patient (Amjadi-Begvand *et al.*, 2004). Information obtained about the duration of the disease will clearly be subject to considerable error, especially in cases where a person had been suffering for a long time (Fellingham *et al.*, 1973). In general, OAs have a 'window period' where treatments have the best outcomes in preventing joint damage, decreasing functional disability and limiting pain. During the window period, a more aggressive treatment regimen is more likely to succeed than the same treatment applied later in the course of disease (O'Dell, 2002; Boers, 2003; Amjadi-Begvand *et al.*, 2004). MJD also has a small window of opportunity for therapy to ensure that patients regain joint function and mobility, and reduce pain (Fredlund, 2003). Delays in treatment provision for patients with OA have been associated with an increased rate of joint degeneration and physical disability (Amjadi-Begvand *et al.*, 2004; Ozgocmen *et al.*, 2009). Improving the diagnostic procedure and detection of this condition would be beneficial to disease outcomes by preventing advanced joint degeneration and avoiding costly interventions like joint replacements.

Several interviewed doctors reported being uncertain about their ability to differentiate between MJD and generalised OA. The confusion linked to diagnosing MJD speaks to the lack of training provided to the new staff at the Mseleni Hospital. While several doctors referred patients with joint pain to more experienced colleagues, they expressed wanting to be empowered to diagnose MJD and provide effective care to their patients. A mentorship and an orientation programme for new doctors may benefit incoming doctors by introducing them to MJD, and the management strategy employed at the Mseleni Hospital. At present, doctors at the Mseleni Hospital attend morning meetings where difficult cases are presented and discussed with colleagues (Fredlund, 2010). One of the suggestions given by several doctors new to the Mseleni Hospital was that practitioners from the Orthopaedic unit present MJD cases on a weekly basis to allow new doctors to become familiar with the diagnostic and treatment protocol.

Pain reduction and joint mobility are the primary focus of treatment during the initial stages of MJD. In addition, therapeutic interventions to maintain joint movement and function were prescribed for 57% of MJD patients. Interviewed doctors noted the usefulness of pain management to restore mobility and ensure that patients were able to move the joint to prevent joint-freezing and complete immobility. Doctors emphasised the importance of physiotherapy in addition to pain management. This

differed in the discourse on treatment in MJD patients. Non-adherence to physiotherapy occurred in 65% of MJD patients, and no association was found between the patient's age and adherence. When interviewed patients were asked about their physiotherapy attendance, several noted the therapy resulted in increased pain and they stopped going. Another reason for poor adherence may be remoteness of a patients home and distance to the hospital or clinic where they receive care.

Patients focussed largely on taking their medication to relieve pain, believing that physiotherapy was harmful to them because it resulted in more pain. Chronic joint pain and stiffness were managed with NSAIDS (like aspirin, brufen, indocid, diclofenac and naproxen) and paracetamol/tramadol. Interviewed patients were largely unaware of the medications they were taking, and largely referred to them by colour as 'the blue ones' or by joints they helped relieve, for example 'the knees'. The disconnect in language used to refer to treatment by MJD patients and doctors was apparent from interviews. Doctors recorded clinical names and frequently spoke about medication types during interviews, whereas patients were unable to name the medication they were taking for MJD or differentiate between this medication and treatments for other conditions. The illicit trade of pharmaceuticals was cited as a concern in treating MJD safely and effectively. This is an area that requires further work as this is likely to impact the treatment of several conditions treated at the Mseleni Hospital.

Several doctors reported administering cortisone injections to knee or shoulder joints to relieve inflammation-associated pain and stiffness in MJD patients. Evidence of this treatment was, however, only found in the medical records of one of the MJD patients sampled in this study. This is not necessarily contradictory as cortisone injections are not commonly used in cases of advanced joint degeneration (Arroll & Goodyear-Smith, 2004). A meta-analysis on the efficacy of corticosteroid injections for treating OA in the knee reported reduction of symptoms for 2-24 weeks in patients with disease duration of 24 months-9.8 years (Arroll & Goodyear-Smith, 2004). The conclusions were that the maximum efficacy of steroidal injections occurs in patients with shorter disease durations (Arroll & Goodyear-Smith, 2004). The lack of steroidal use in treating inflammation in MJD patients could be because patients are receiving these injections at clinics that were not sampled as part of this study, or it could be because these injections are most effective at the early stages of joint degeneration and the patients sampled in this study had disease durations spanning more than 5 years.

From medical records and surveys, a negative association was identified between joint arthroplasties and age ($p=0.03$), as older patients were less likely to undergo surgery or even receive a referral for surgery. Reluctance of elderly persons to receive operations is common in generalised OA patients (Fredlund, 2003). During interviews, several patients cited their age as reasons they would not undergo another joint replacement. Interestingly, this may be linked to past traumatic experiences (as noted by three patients) or even difficult recovery (cited by one patient). Approximately 23% of patients

from the medical record reviews had a single joint replacement, while 6% had multiple operations including revision surgery, with the hip and then the knee being the most frequent replacement sites. Patients reported improvement of function and mobility after joint surgeries, and Fredlund (2003) reported statistically significant and clinically satisfying improvements in patients undergoing total hip replacements. Our study found that 6% of MJD patients had undergone revision or salvage operations to achieve pain relief without further limiting functionality or mobility in the affected joint. This was similar to findings of Fredlund (2003). A deeper look into the reasons that MJD patients choose not to undergo surgery would be interesting and useful in providing patients with effective management and care.

The difficulty of joint replacements in MJD patients was cited by several interviewed doctors who believed arthroplasties to be complicated by the advanced destruction and unique hip morphologies and acetabular sizes in MJD patients. In our study, doctors noted the demands of rural lifestyle were limiting to the longevity of prosthetics, similar sentiments were discussed by patients. Fredlund (2003) reported that patients between the ages of 30-40 years that received joint replacements had good mobility, but due to considerable physical demands on their joints, required frequent prosthetic replacement. Despite considerable advances in prosthetics over the last twenty years, more work towards developing prosthesis and post-care programmes tailored for rural communities is needed. While small acetabular joints have been reported in MJD patients (Lockitch, 1974; Du Toit, 1979; Sokoloff *et al.*, 1985), the role of this in the pattern of pathology remains unknown.

The lack of continuity of care and fragmentation within the healthcare system were cited by doctors as the greatest barriers to treating MJD effectively. Three doctors noted the lack of continuity of care due to the fragmentation between the record keeping at the clinics and the hospital, suggesting that the unstandardised record keeping between the clinic and hospital prevented them from being able to follow up on patients. Several doctors suggested this could be improved by having a team of doctors and nurses dedicated to following up MJD patients from the clinic to the OPD. As radiographic equipment is only available at the Mseleni Hospital, patients with joint pain are required to travel for radiographs. While transport is provided twice a day to-and-from the hospital for several clinics, the lack of designated staff to manage MJD patients means the referral process is lengthy, with limited follow up (Waller, 1998). Doctors and nurses noted that referrals to the Mseleni hospital often limited individual follow up and continuity of care as patients had to wait several hours for X-rays and would need to receive treatment from a different doctor than the one that referred them for tests. Long waiting times in public hospitals in South Africa have been linked to delayed care-seeking.

4.4.1 The impact of COVID-19 on MJD

The second phase of data collection took place several months after the first wave of the SARS-CoV-2 (COVID-19) pandemic in South Africa. During this time, hospitals postponed operations and procedures for non-life-threatening conditions like MJD. Several patients reported not keeping appointments for check-ups due to fear of COVID-19 and one patient with bilateral hip immobility reported having a hip replacement postponed due to the pandemic. While doctors noted that patients were provided with continuous care and follow-up during the COVID-19 period, it is plausible that hesitance to visit the hospital likely prevented new and existing patients from seeking care. Further work is needed to explore the impact of the circulating epidemic on primary healthcare provision in the region and the long-term impact this has on MJD outcomes in the region. Coping with MJD amidst the current pandemic would be a challenge especially due to issues in supply shortages and lack of access to health facility and health care providers. It is expected that lockdown might have affected the management of routine diseases such as MJD, but an in-depth analysis of this was beyond the scope of this study.

4.5 Explanatory models and treatment-seeking behaviours of MJD

Interviews with MJD patients included stories about the experience of living with MJD, with references to chronic pain, loss of livelihood, joint replacements, disability and loss of independence. Explanatory models of MJD were variant between patients, nurses and doctors. Patients generally invoked supernatural (witchcraft or ancestral displeasure), natural (nutritional deficiencies, and/or environmental); and/or social (gender-based practices and lifestyle) beliefs explanatory models. In contrast, doctors primarily focussed on environmental and social theories of causation, while nurses represented an intersection between these two groups, invoking spiritual, environmental and social explanatory models. Interestingly, doctors and nurses cited multiple causes of MJD, while patients largely cited singular factors drawing contrast between biomedical perspectives of causation being multifactorial versus traditional beliefs of singular causes for conditions (Valles, 2020). It is well-reported that patients tend to form their own explanatory models for illnesses, these are often incommensurate with scientific beliefs (Jimenez Fernandez *et al.*, 2018; Liyange, 2019; Venugopal *et al.*, 2014).

Patients most commonly cited soil as the cause of MJD and linked this to their experience of joint pain and limited movement while walking on the soft sandy soil in the region. Several patients and nurses believed that doctors and researchers had determined that MJD was caused by the soil in the region. This theory surrounding causation is grounded in TAM conceptualisations of illnesses that are symptom-focussed (Edwards, 2010; Sobiecki, 2014). Thus, when pain is experienced while walking on soil the disease is suspected to be caused by the soil. Given this association, the belief that MJD is

caused by *umeqo* (these are caused by stepping over the harmful creation of a sorcerer) is symptoms of pain and disability while walking. Patient-held beliefs that MJD is caused by the soil in the region correlate with the higher prevalence of MJD in the sand-forest zone in the area. While the elemental and nutrient composition of the soil in the affected area have been assessed, no aetiological associations have been identified (Lubbe, 1973; Ceruti *et al.*, 2003). The link between MJD and the sand-forest zone detected in interviews, surveys and medical records is interesting and may suggest that joint stress and strain due to walking in sandy soil contributes to the pattern of pain and pathology seen in MJD.

Patients were aware of community-wide beliefs about the spiritual causes of MJD but were reluctant to share these during interviews. In addition, patients denied using TAM to treat MJD despite the presence of scars (*caba* marks) on their knees, and arms. The reluctance to share information about TAM practices has been discussed by Pemunta & Tabenyang (2020b), Sobiecki (2014) and Washington (2010). One of the reasons for this may be because I was not a local to the culture or region and participants felt mistrust or discomfort sharing their use of TAM with someone affiliated with WBM (this limitation will be discussed at the latter part of this chapter). Patients openly shared their experiences of WBM treatments at the Mseleni Hospital, suggesting that they saw me as part of that context and were more comfortable to share about that. TAM healing practices are profoundly linked to land, ancestors and community and they are not commonly shared with those who do not share this context (Washington, 2010). One patient, however, openly discussed her experience of using *caba* (incisions and *muthi*) prior to seeking care at the Mseleni Hospital. The dual use of WBM and TAM is not unique to this region or condition, and is common in SA (Edwards, 2010; Washington, 2010; Pemunta & Tabenyang, 2020b). As Ashforth (2005) notes, the dual use of TAM and WBM implies that both provide the patient with some level of comfort, healing and relief from illness.

Patients reported non-adherence to physiotherapy as they felt that the increased pain during therapy sessions suggested the treatments were not helping. This suggests that MJD patients appraise their treatments based on their relief of symptoms and cure, as physiotherapy did neither – patients believed the treatment was unsuccessful (Kleinman *et al.*, 1978). This reflects the need to understand culturally constructed explanatory models of illnesses and their treatments so that care-strategies can be communicated clearly (Kleinman *et al.*, 1978; Jimenez Fernandez *et al.*, 2018). Poor communication and patient-doctor relationships can have a have a negative impact on how the patient experiences healthcare and often the outcomes of their conditions (Martorell *et al.*, 1976; Amjadi-Begvand *et al.*, 2004). Various factors are known to impact communication between healthcare provider and patient, these are gender differences, language differences, the noise within the ward, age differences and family presence and involvement (Norouzinia *et al.*, 2015). In many South African hospitals doctors who are largely English or Afrikaans speaking are unable to clearly communicate with patients who exclusively speak Southern African Bantu-languages. The lack of formal interpreters

means that doctors largely rely on nurses, hospital clerks and other staff to translate and facilitate communication (Schlemmer & Mash, 2006). Several doctors interviewed in this study reported barriers in communication due to reliance on translators (Appendix D). In these contexts, patients are robbed of their power due to inability to independently ask questions or discuss their treatments (Schlemmer & Mash, 2006). Given that clear communication is central to improving treatment adherence, the process of improving communication between doctors, nurses and patients at the Mseleni Hospital requires further scrutiny.

One suggestion made by several doctors to improve the treatment of MJD was the addition of training in how to diagnose and treat MJD for new arrivals to the Mseleni Hospital. The benefit of this to the hospital is notable as doctors treat MJD with limited knowledge of MJD as this is not part of curriculum taught at universities. At present, doctors at the Mseleni Hospital attend morning meetings where difficult cases are presented and discussed with colleagues. One of the suggestions made by doctors new to the Mseleni hospital was that the doctors in the Orthopaedic Unit MJD cases on a weekly basis to allow new doctors to become familiar with the diagnostic and treatment protocol. Another suggestion for improving the diagnosis and treatment of MJD was the development of a standardised *proforma* for MJD. Several studies reported improvements in the diagnosis and management of OA after a standardised proforma was introduced in a clinical setting (Günther & Sun, 1999; Gensler *et al.*, 2008; O'Shea *et al.*, 2009). By providing clinicians with standardised templates to assess symptoms, pathology and evaluate treatment strategies, patient outcomes were consistently improved, regardless of the clinician's experience. As the Mseleni hospital has a high turnover rate of doctors due to its status as a teaching hospital, a *proforma* for MJD may improve the diagnosis and treatment of this disease. Generating a *pro forma* for diagnosing MJD is a cost-effective strategy to ensure standardised treatment for patients with this condition.

Doctors at the Mseleni hospital were well informed about TAM healing practices but described these as unscientific and at times harmful. They emphasised the lack of regulation and predictability of traditional healing as a shortcoming preventing WBM and TAM from working together. While professional bodies play a critical role in the institutionalisation and regulation of WBM, their application to TAM negates the importance of the indigenous knowledge, heritage, culture and spiritualism that shapes TAM (Washington, 2010; Pemunta & Tabenyang, 2020a). Biomedical doctors interviewed in this study showed a willingness to use traditional medicines if they were well researched and understood but expressed concern that this may give socially and physically harmful healing practices further credibility in the community. This attempt to restrict TAM to the confines of WBM theory and practice, has been described as a form of WBM hegemony (Pemunta & Tabenyang, 2020b). It has been argued that the widespread use of TAM, and its combination with WBM in SA, implies the potential for both these systems to be integrated into the healthcare system (Pemunta & Tabenyang, 2020a). In its current state, the healthcare system in SA cannot accommodate both forms of medicine,

as their approached to illnesses are polarised – with WBM finding credibility in evidence, experimentation and generalisation – while TAM finds credibility in community acceptance, experience-based knowledge and lack of generalisability.

Loss of education, unemployment and financial pressure due to treatment costs were cited as economic consequences of MJD. While specific health related initiatives such as WBM healthcare, assistive devices and therapy are provided for MJD patients, many patients are unable to adapt their homes or lifestyles to compensate for the loss of mobility. As has been noted by Johannsmeier (2007), in rural KZN the costs of social inclusion are not identical for people with physical disabilities as additional money is often required to overcome barriers of disability (for example, some disabled people in rural KwaZulu-Natal regions report paying up to R150 for a trip in a private hired car, as compared to the normal taxi fee of under R10 (Johannsmeier, 2007). Considering that the disability grant is only R1500, people affected by MJD are more likely to pay proportionally more to accomplish similar tasks. Unlike state-funded WBM consultations, TAM consultations can cost patients over R500 per consultation (Washington, 2010; Pemunta & Tabenyang, 2020b) - making this a costly pursuit for MJD affected patients. Given the limited income in MJD affected families, further research into the financial costs associated with TAM and WBM in the affected area is needed.

The psychosocial impact of MJD included loss of independence, strained interpersonal relationships and stigmatisation due to the inability of affected individuals to continue daily chores or to fulfil social expectations. The impact of MJD on sexual intimacy was a surprising finding that requires further investigation. Patients sited loss of financial and physical dependence as their greatest concern, with several noting financial and physical reliance on their daughters or daughters-in-law (*makoti*'s). . Loss of self-reliance and chronic pain in patients with arthritis has been cited at as a primary cause of depression in patients in a resource constrained community in the Dominican Republic (Niu *et al.*, 2011). Further work is required to assess the prevalence and impact of depression on patients with MJD.

In interviews, doctors noted younger patients between the ages of 40-50 years old were more likely to be stigmatised for MJD and have more unmet needs than older patients. This was because these patients did not meet social expectations linked to their age or position within households. Harling *et al.* (2020) reported that SABP patients suffering from physical impairments, below 60 years of age had a higher rate of unmet need than those above 60 years. This led to the suggestion that this may be because younger patients do not meet the stereotype of requiring care, or that care-givers in middle-aged individuals may be older parents who may not be able to provide care due to impairment themselves (Harling *et al.*, 2020). Hazell (2010) explains that *makoti*'s are expected to provide care for their children, spouse and in laws, and that daily care provision from the public and private sector is not common. Several doctors cited concerns regarding social expectations and pressures on *makoti*'s in the

region. The role that spouses, *makoti's* and adult children play in meeting the care-needs of MJD patients requires further exploration

4.6 Study limitations

Linguistic and sociocultural barriers impacted the communication between patients, interviewers and doctors at the Mseleni Hospital. The transcription and translation processes may have missed some subtle aspects of language and culture. My position as a white, woman, who does not speak Zulu impacted the communication and trust between participants and myself. It is conceivable that the study participants were cautious about what they shared with me during interviews, leading to reporting bias. To minimise discomfort and mistrust, translators that were local to the affected region and were familiar with the culture, language and region were recruited. In some cases, the translator asked some of the closed response questions in a leading manner, like “You come from the Mseleni area, right?”, this mainly occurred with closed response questions, and was only detected subsequent to data collection and translation. As a result, the impact of this information on results was deemed negligible. Several interesting answers provided by patients could not be probed or explored further during interviews as recordings were only translated prior to study. Despite these limitations, our study demonstrates the value of using pre-survey work and interviews to ensure that survey design that effectively represent patient perspectives of MJD. This is evidenced by the fact that patients provided answers that were clear and easy to understand, and that subsequent phases of interviewing provided themes that supported the models from the survey-development phase.

While I endeavoured to obtain information as an objective observer, my status as a researcher and an outsider to the region, likely impacted the way that doctors, nurses and patients interacted with me. Throughout the analysis process, I was aware that my Western biomedical conceptions of illness and disease could influence my interpretation of interviews of patients, doctors and nurses. To mitigate the effects of this potential bias on this study, I worked directly from the interview transcripts, rather than from our overall interpretations of patients' words and interviewer notes. In addition, all codes and themes were discussed with the principal investigator of this study to ensure that conclusions arrived at were from the data and not my own interpretation.

A cross-sectional assessment of the point prevalence of MJD at the OPD at the Mseleni Hospital in May 2019 was conducted. This sampling strategy was selected as the Hospital lacks an electronic record keeping system and thus, screening medical records for MJD prevalence manually was required. This limitation prevented a large-scale retrospective medical record review to assess annual prevalence of MJD. As MJD affected and unaffected individuals were sampled at the Mseleni Hospital, the MJD negative or unaffected group may not exclusively represent a healthy cohort or even the underlying population affected by MJD. Thus, the prevalence estimated in this study represents the burden of MJD on the Mseleni Hospital and not necessarily all individuals from the uMkhanyakude region.

As doctors surveyed in our study reported a lack of confidence in their ability to differentiate between generalised osteoarthritis and MJD, it is conceivable that MJD diagnoses were underrepresented in the medical records. We minimised this potential bias by including all patients with bilateral hip and knee osteoarthritis and a listed MJD-diagnosis as MJD-positive patients. Given the findings in our study that many patients experience onset unilaterally in their ankles, knees and then hips – our use of bilateral hip pain and pathology as an indication of undiagnosed MJD may underestimate the prevalence. As our study was more likely to detect advanced cases of MJD, younger patients were less likely to be detected. The absence of International Statistical Classification of Diseases and Related Health Problems (ICD) - 10 codes in the medical records limited our ability to assess whether similar or repeating codes were used when referring to MJD-patients.

While the medical records lacked formal diagnoses for some patients, we cannot exclude the possibility that our sample of MJD negative patients may include some individuals yet to be diagnosed MJD. Furthermore, individuals experiencing the onset of MJD or limited pain, and those self-treating or seeking care from other sources are not likely to be sampled in our medical record review. While a larger epidemiological survey is desirable to overcome several of the abovementioned shortcomings, this was not feasible within the timeframe or budget of this research. Access to medical records at the Mseleni Hospital was limited by the complexities of the clerical system and absence of medical records due to patient transfers. Inconsistent record keeping was an issue in medical records, and in some cases, patients had multiple files, while other patients had no files available for review. Introduction of an electronic medical record system is practically complicated and costly but may significantly improve clerical errors in the curation of medical records at the Mseleni Hospital. The lack of standardised reporting prevented comparing onset time and mode of onset of MJD between medical records, surveys and interviews.

Inconsistencies associated with the curation of medical records and the lack of standardised reporting may have limited the detection of co-morbidities associated with MJD. This may be because WBM facilities are primarily problem-focused and local categorizations of illness may not fall be deemed biomedical “problems”. The absence of brachydactylous dwarfism in the medical records was notable and only 2 dwarfed MJD patients were interviewed. While no significant differences in responses were identified between patients with brachydactylous dwarfism and those of regular stature, the findings in our study are unlikely to be generalisable to dwarfed patients with MJD. The fact that brachydactylous dwarfism, was absent from all medical records assessed in this study may be due to the shortcomings of the record keeping system at the hospital, or because our study was not powered to detect which has a prevalence of 0.1 % in the population. The failure of health information systems (medical records) to capture locally-constructed health experiences was notable, and we attempted to address this through inclusion of interviews. Our meta-analysis only yielded only four studies, that matched the inclusion criteria. A larger sample of papers for the meta-analysis is preferred, but the

limited epidemiological literature on MJD prevented this. While the results in our study may be relevant to other conditions they are not necessarily generalisable to other joint diseases as MJD is an endemic disease.

4.7 Future work and recommendations

Future work should include a more comprehensive epidemiological survey and medical record review of MJD. This is required to further elucidate the role that socio-economic conditions, resource acquisition and socio-cultural practices play in the onset and experience of MJD. A comparison between MJD and joint pathology in rural regions in South African is needed to determine if patterns of disease expression are consistent with those across rural South African regions.

A longitudinal cohort study of at-risk patients (specifically those with a family history of MJD) is needed to assess the incidence, prevalence, onset age and mode of onset, as well as risk factors of MJD. A study spanning several years is needed to track the onset of joint degeneration and pathology to using radiographs and the correlation with patient-reported pain. The role of role of PA and MED in the pathogenesis of MJD should also be further explored, with potential for assessing the aetiological role of joint shape and size (Lockitch, 1974; Du Toit, 1979; Sokoloff *et al.*, 1985). Future work should be expanded to assess the prevalence of MJD in dwarfed patients, and to determine whether any differences exist in the clinical and social experience of MJD.

While no evidence of mendelian inheritance has been identified in MJD patients (Lockitch, 1974; Ballo, 1998), complex genetic mechanisms such as imprinting, epistasis and polygenic susceptibility may be operative in families and individuals affected by MJD. Whole genome sequencing and ribonucleic acid (RNA)-sequencing may help identify epigenetic factors critical to cartilage, bone and synovium development and maintenance that may be aetiological of MJD (Ballo *et al.*, 1998; Gibbon *et al.*, 2010).

Further work is needed to explore the process of onset recall in MJD-patients so that physicians can be better equipped to assess onset in patient interviews. Assessing MJD onset should be expanded by including categories of onset types (such as gradual, acute, widespread) based on the extent of pain and immobility at onset. Interviews with patients refusing surgery and physiotherapy at the Mseleni Hospital is needed to better understand decision-making processes so doctors and nurses can better facilitate care and healing. Improving the diagnostic procedures and detection of this condition would be beneficial to disease outcomes by preventing advanced joint degeneration and avoiding costly interventions like joint replacements. As the Mseleni hospital has a high turnover rate of doctors due to its status as a teaching hospital, a *pro forma* for MJD may improve the diagnosis and treatment of this disease. Generating a *pro forma* for diagnosing MJD is a cost-effective strategy to ensure standardised

treatment for patients with this condition. The standardisation of ICD-10 codes at the Mseleni Hospital will be beneficial in ensuring consistent diagnoses and may facilitate statistical monitoring of MJD in the region.

The importance of understanding individual experiences of MJD and communal disease narratives was evident from our study. While differences in explanatory models were identified between MJD patients and healthcare providers, further expansion of our sample to include younger patients is necessary. The impact of education, age and socio-economic development on explanatory models and treatment-seeking behaviours is needed. Our study primarily focussed on WBM healing, and interviews should be expanded to explore local perceptions of TAM and WBM through inclusion of community leaders, traditional healers, household heads and MJD-patients. Given the limited income in MJD affected families, further research into the financial costs associated with TAM and WBM in the affected area is needed. More research into unmet care-needs of MJD patients of different areas, ages and genders is required to assess the role of the healthcare system, spouses, *makoti's* and adult children in meeting the care-needs. This should involve exploration into the domestic burden of MJD on women from households that are poor or disadvantaged as technology, transport and money may alter the social dynamics of access.

Chapter 5: Conclusion

MJD is a crippling osteoarthropathy that is geographically localised to a remote group of SABP in Northern KwaZulu-Natal, South Africa (Wittman & Fellingham, 1970). As MJD progresses, those affected lose the ability to perform everyday activities independently, resulting on reliance on personal care from family, friends or neighbours and financial dependence on social assistance grants and family sources of income (Mann & Fredlund, 1988; Waller, 1998). The generational impact of MJD on families and the wider community is seen in the burgeoning rates of unemployment and physical disability in the MJD-affected region. From a review of the literature, it was evident that research into risk factors, explanatory models and treatment-seeking behaviours linked to MJD was needed to formulate care strategies that mitigate the burden of MJD on individuals, families, local communities and the regional healthcare system. This study used a biocultural approach was used to assess biological, social and cultural risk factors of MJD and the interactions between these factors and conceptualisations and experiences of this disease. A mixed methods study was used to provide insight into the MJD phenomena from the perspective of patients, nurses and doctors at the Mseleni Hospital.

A point prevalence estimate of 9% was obtained for MJD using medical records at the OPD. Our findings provide an essential update on the point prevalence of MJD and indicate that this condition remains a significant burden on the OPD of the Mseleni Hospital. There was no consensus about the events leading to the onset, the stage of life, or age patients first experienced joint pain, and the variability in onset age/period may be an artefact of the gradual and insidious initiation of MJD. The initiation of MJD occurred exclusively in the appendicular skeleton with secondary pathology identified in the axial region. The pathology reported in the shoulder and elbow joints of MJD patients is the attributable to altered gain and reliance on walking aids as the condition worsens. Evaluating onset of arthritic conditions like MJD is notoriously difficult, a long-term study of at-risk patients (with a family history of MJD) is needed to determine when the onset of pathology occurs and if this correlates with patient-reported pain. A better understanding of the onset recall process is needed to ensure that doctors maximise their understanding of the onset and rate of progression so they can plan a management strategy for their patients.

Our research confirmed a later onset age of MJD in patients over the age of 35 years old. The change in MJD onset identified temporally from the meta-analysis may be evidence of a temporal change in an aetiological factor. This is in agreement with suggestions by interviewed doctors that MJD may be a generational condition that had a declining incidence. Alternatively, this result may be because of our sampling strategy favoured patients with more severe forms of MJD, seeking care at the Mseleni Hospital. Patients experiencing a mild onset of symptoms or treating their symptoms through self-medication or other forms of medicine were less likely to be at the Mseleni Hospital seeking care. The

fact that MJD patients only seek care when this disease becomes incapacitating may be linked to mistrust of the healthcare system or healthcare providers, limited access to healthcare, transport or lack of knowledge about how the potential benefits that early detection and treatment can have on the prognosis. From interviews, it was evident that patients first attempted to treat MJD with TAM before WBM, providing another explanation for the WBM latent care-seeking noted in MJD patients

Age confounded the association between MJD and gender, suggesting that age-linked differences between men and women may be contributing to MJD. We suggested a possible causative link between MJD and lower oestrogen in aging women, as lower oestrogen in menopausal women has been shown to worsen joint degeneration. The prevalence of MJD in men suggests that while altered oestrogen levels may explain the increased prevalence and severity of MJD in women, this is unlikely to be an essential cause of MJD.

The association between MJD and subsistence farming practices, poor access to transport and reliance on water from rivers suggests that activity-linked stresses in the MJD-area are contributing to joint degeneration. The lower density of MJD patients adjacent to rivers, as assessed from medical records, indicated that proximity to a primary water source is a likely risk factor of MJD. Thus, the clustering of MJD along the sand-forest zone and around the Mseleni Hospital may be because the lack of water in the region, requires frequent collection and loadbearing of water from rivers and water points. Alternatively, it may point to a unique environmental aetiology around the sand forest belt in the region, as few cases have been detected in adjacent environmental zones. Thus far, MJD prevalence surveys have been primarily localised around the Mseleni Hospital, and these results suggest the need for more studies to explore the prevalence in regions northwards of the hospital. The prevalence of MJD in the sand-forest zone is particularly interesting as several patients and nurses believed the sandy soil in the region to be causative of MJD. Activities requiring movement in the soft, sandy soil are suspected to contribute to joint pain, and to the pattern of pathology characteristic of MJD.

Explanatory models and treatment-seeking behaviours in MJD patients were largely informed by TAM. Patients generally invoked supernatural (witchcraft or ancestral displeasure), natural (nutritional deficiencies, and/or environmental); and/or social (gender-based practices and lifestyle) beliefs explanatory models. In contrast, doctors primarily focussed on environmental and social theories of causation, while nurses represented an intersection between these two groups, invoking spiritual, environmental and social explanatory models. Interestingly, doctors and nurses cited multiple causes of MJD, while patients largely cited singular factors drawing contrast between biomedical perspectives of causation being multifactorial versus traditional beliefs of singular causes for conditions. Patients most commonly cited soil as the cause of MJD and linked this to their experience of joint pain and limited movement while walking on the soft sandy soil in the region. Patients also appraised their treatments based on their relief of symptoms and perceptions of cure, as physiotherapy did neither, patients

believed the treatment was unsuccessful. Dual use of TAM and WBM implies that both provide the patient with some level of comfort, healing and relief from illness.

Introducing a *pro forma* for MJD diagnosis and treatment may be useful in ensuring that patients receive standardised treatments and effective management. One of the benefits of a *pro forma* would be that regardless of which doctor the patient sees in follow up visits, their standard assessments of symptoms will be identical. The lack of continuity of care and fragmentation within the healthcare system were cited by doctors the greatest barriers to treating MJD effectively. Patients with non-life-threatening conditions like MJD are often not referred to doctors at the clinic until their pain is unmanageable with analgesia and they are unable to walk. It is expected that lockdown during the Coronavirus pandemic might have affected the management of routine diseases such as MJD, but the burden of disrupted management will only be visible with time. Further work is needed to explore the impact of the COVID-19 pandemic on primary healthcare provision in the region and the long-term impact on MJD outcomes.

There is scant knowledge about the onset and pattern of disease progression, implying that these areas require further exploration. A longitudinal study of individuals-at-risk of MJD (those with a family history of this disease) should be completed by monitoring at-risk patients over several years to determine the incidence of MJD and assess temporality of causative factors. This research study raised several broader issues in the study population, issues which are not strictly linked to the onset or aetiology of MJD but are likely to impact the quality of life of MJD-affected patients. Our work provided insight into the common use of indigenous medicines to treat MJD, yet further work is needed to explore traditional medicinal practices linked to MJD more thoroughly by interviewing community leaders, traditional healers and patients.

This study demonstrated the utility of the biocultural approach in identifying and contextualising biological, social and cultural causes of MJD. In addition, this approach provided insight into how these causative factors are conceptualised and how these conceptualisations condition responses to illnesses.

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Appendices

Appendix A. Publications

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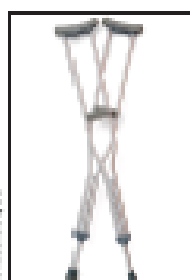
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Comment

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Mseleni joint disease: an endemic arthritis of unknown cause



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In a letter to *The Lancet* in 1970, Wiltman and Fellingham reported an "unusual hip disease" that exclusively affected a rural community of Zulu-language speakers residing in BwaZulu-Natal, South Africa.¹ This condition is locally known as unyonga, meaning a disease of the joints, but was clinically named Mseleni joint disease because of the localisation of affected individuals around the Mseleni Mission Hospital in Mseleni, South Africa.² Weight-bearing surfaces of joints are mostly affected but a unique diagnostic feature is the bilateral occurrence of hip pathology, which frequently includes pelvic shape deformities. Individuals with Mseleni joint disease have chronic joint pain, limited mobility, and inevitably severe physical disability, impacting regional health care and social welfare systems, which are already heavily burdened by HIV and tuberculosis. Over the past 50 years, several cultural, pathogenic, environmental, and genetic causes have been investigated, yet the cause of Mseleni joint disease remains unknown.³ The unequivocal link between cultural practices, socioeconomic conditions, and the pattern of bone and cartilage pathology associated with Mseleni joint disease suggests a multifactorial cause.³

The geographical localisation of Mseleni joint disease to this community is strange as genetic evidence, historical records, and oral histories suggest that the affected population is neither genetically nor culturally different from other Zulu-language speakers in South Africa.⁴ The demographic distribution of Mseleni joint disease was last assessed in 1973 and 1985.^{4,5} The prevalence was conservatively estimated to be 5-1% in 1985.⁴ Women were reported as three times more likely to have the

disease than men.^{4,5} Although Mseleni joint disease has been reported in children and adolescents, diagnoses most frequently occur in individuals between 60 and 70 years old.^{1,4} Despite a paucity of literature on Mseleni joint disease prevalence, over the past 10 years, physicians at the Mseleni Hospital have noted a decreased incidence and increased age of diagnosis.

Mseleni joint disease has been described as a bilateral, uniform osteoarthropathy that is mostly localised to the hip region, although pathology has been noted in other synovial joints. The occurrence of narrowing interarticular spaces, subarticular sclerosis, and osteophytes resembles various osteoarthropathies, but the bilateral pattern of hip pathology is unique to Mseleni joint disease.⁶ In the absence of discrete diagnostic criteria, Mseleni joint disease is identified by excluding other joint or bone conditions such as rheumatoid arthritis, gout, reactive arthritis, and avascular necrosis. Diagnosis is further complicated by the fact that affected individuals generally have a combination of several skeletal deformities, including protrusio acetabuli, multiple epiphyseal dysplasia, and flattening or so-called mushrooming of the femoral head with subluxation.⁶ These clinical features have led to the suggestion that Mseleni joint disease comprises two subtypes distinguishable by the presence of multiple epiphyseal dysplasia and protrusio acetabuli.⁶ This classification, however, does not account for the asymptomatic occurrence of these variations in individuals who are non-arthritic and their comorbidity in patients with Mseleni joint disease. The homogeneous pattern of cartilage degeneration in individuals with

different pelvic shape deformities begs the question: Is Mseleni joint disease caused by cartilage or synovial degeneration or by abnormalities in bone morphology?

The heterogeneous clinical presentation and the poor understanding of the molecular mechanisms that underlie pathogenesis in this disease have impeded the development of screening methods and treatment. Although the onset of Mseleni joint disease is asymptomatic, patients eventually have painful, stiff, and limited joint movements and crepitus (clicking sounds during movement) leading to dependence on walking-aids for mobility.³² Not surprisingly, the first interventions for Mseleni joint disease are aimed at reducing pain and restoring joint function.⁴ Non-steroidal anti-inflammatory drugs are successfully used to alleviate joint pain, however, patients generally report little improvement in their mobility.⁴ As a short-term solution, such drugs are affordable and effective with few contraindications, however, the long-term risks of chronic pain medication use are well reported and include systemic organ damage, internal bleeding, cardiovascular disease, and gastrointestinal problems. Although surgical interventions, like total hip and knee joint arthroplasties, have been an effective option for pain reduction and improved mobility, these are costly to the health-care system.⁴ Physiotherapy treatments provide some pain relief and improved mobility, however, low adherence to these treatment programmes necessitates improved disease awareness and engagement between affected individuals and the health-care system.

Individuals with Mseleni joint disease are forced to rely on disability grants and their families for subsistence and this reliance ultimately hinders socioeconomic development in this region.³ It is estimated that 50% of individuals between the ages of 6 and 25 years who have parents with Mseleni joint disease have no formal education, compared with only 30% of those with unaffected parents in the same community.⁴³ Because of the cultural partitioning of labour, young people, especially girls, frequently forgo school to assist with familial care and household subsistence. This imbalance further perpetuates poverty and gender inequality in this region as few economic opportunities are available for those with a poor education. The socioeconomic consequences of Mseleni joint disease are far-reaching, impacting the lives of patients and their families. Some affected individuals receive meagre disability grants of approximately ZAR1780 or US\$125 a month, which are used to financially support extended families.³³ Although

some reduction in the social burden of this disease has been achieved through community interventions, further efforts towards community development, access to social grants, and support for families could substantially reduce the socioeconomic burden of Mseleni joint disease on the community.

A collaboration is underway between the University of Cape Town (Cape Town, South Africa), Yale University (New Haven, CT, USA), and Mseleni Hospital (Mseleni, South Africa) to investigate the molecular pathogenesis of Mseleni joint disease with use of advanced sequencing to identify genes with altered expression in Mseleni joint disease, and three-dimensional models of patient-specific cartilage and bone to test the role of these genes. An epidemiological assessment of the present-day distribution, perception, and prognosis of disease has been completed. Involvement of patients, physicians, community leaders, scientific, and government stakeholders is required to facilitate a holistic understanding of the cause of this disease.

Elizabeth S Dinkelé, Robert Ballo, Victor Fredlund, Raj Ramesar, Victoria Gibbon



Department of Human Biology (E.S.D., R.B., V.G.) and Division of Human Genetics (R.R.), University of Cape Town, Cape Town 7935, South Africa; and Mseleni Hospital, Sibhayi, KwaZulu-Natal, South Africa (V.F.)
victoria.gibbon@uct.ac.za

We declare no competing interests. We thank the National Research Foundation for financial assistance on this research. Opinions expressed, and conclusions arrived at, are those of the authors and are not necessarily attributed to these funding bodies.

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Figure A1. Journal article published in the *Lancet Rheumatology* by Dinkelé, E.S., Ballo, R., Fredlund, V., Ramesar, R. & Gibbon, V., titled: “Mseleni joint disease: an endemic arthritis of unknown cause.”

Appendix B. Ethics approvals

| | | |
|---|--|---|
|  | <p style="text-align: center;">UNIVERSITY OF CAPE TOWN Faculty of Health Sciences Human Research Ethics Committee</p> |  |
| | | <p>Room E53-46 Old Main Building Groote Schuur Hospital Observatory 7925 Telephone [021] 406 6626 Email: shuretta.thomas@uct.ac.za Website: www.health.uct.ac.za/fhs/research/humanethics/forms</p> |

12 March 2019

HREC REF: 079/2019

Dr Victoria Gibbon
Human Biology
Clinical Anatomy and Biological Anthropology
Anatomy Building

Dear Dr Gibbon

PROJECT TITLE: EXPLORING THE AETIOLOGY OF MSELENI JOINT DISEASE (PHD CANDIDATE - MS E DINKELE) SUB-STUDY LINKED TO 822/2015

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 March 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)


Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Elizabeth Dinkele will also be involved in this study.

Yours sincerely



PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 079/2019

Figure B1. Ethics approval from the University of Cape Town Human research ethics committee for the present study.



KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE: MEDICAL

Postal Address: P.O. Sibhayi, Sibhayi, 3967

MSELENI HOSPITAL

Physical Address: Mseleni Hospital

Tel: 035 574 1004 Fax: 035 574 1100

Email address: Mseleni.hospital@kznhealth.gov.za

www.kznhealth.gov.za

ENQUIRIES: DR L.L HOBE

DATE: 24 NOVEMBER 2020

EXT: 103

DEAR MRS DINKELE

RE: APPLICATION TO AMEND AN ONGOING STUDY

Thank you for your application to the Mseleni research ethics committee. We do note the unplanned delays in the committee meeting for your application due to unforeseen circumstances, for this we apologise.

I have the pleasure in informing you that your proposed amendments have been accepted by the Mseleni hospital ethics committee. We do wish you the best in your studies and future prospects.

Please be aware that your study findings will be of value to this hospital and therefore you are requested to share any valuable findings with this committee.

Yours sincerely

Dr L.L Hobe

Chairperson research ethics committee

Mseleni hospital



Figure B2. Ethics approval from the Mseleni Hospital research ethics committee for the present study.



health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge
Management

NHRD Ref: KZ_201902_002

Dear Mrs E. Dinkele
University of Cape Town

Approval of research

1. The research proposal titled '**Exploring the aetiology of Mseleni Joint Disease (MJD)**' was reviewed by the KwaZulu-Natal Department of Health.

The proposal is hereby **approved** for research to be undertaken at Mseleni Hospital.

2. You are requested to take note of the following:
 - a. Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
 - b. Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.
 - c. Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge

Chairperson, Health Research Committee

Date: 03/04/19.

Fighting Disease, Fighting Poverty, Giving Hope

Figure B3. Ethics approval from the KwaZulu-Natal Health Research Committee for the present study.



health

Department:
Health
PROVINCE OF KWAZULU-NATAL

304 Ntsinde Road, Jozini, 3969
PB X026, Jozini 3969
Tel: 035 572 1327 Fax: 035 572 1245 Email: hervey.williams@kznhealth.gov.za
www.kznhealth.gov.za

DIRECTORATE:

District Clinical Specialist Team
Umkhanyakude Health District Office

**Enquiries : Dr CH Vaughan Williams
Telephone : 035-5721327 Ext 114**

4 April 2019

Dear Elizabeth Dinkele,

I have pleasure in informing you that permission has been granted to you by the District Office to conduct research in this district, entitled:

'EXPLORING THE AETIOLOGY OF MSELENI JOINT DISEASE'

Please note the following:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Please ensure this office is informed before you commence your research.
4. The District Office will not provide any resources for this research.
5. You will be expected to provide feedback on your findings to the District Office.

Sincerely,

C H Vaughan Williams
Family Physician, Umkhanyakude Health District Office

Fighting Disease, Fighting Poverty, Giving Hope

Figure B4. Ethics approval from the uMkhanyakude district health office for present study.



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

16 February 2016

HREC REF: 822/2015

Dr V Gibbon
Human Biology
Anatomy Building

Dear Dr Gibbon

PROJECT TITLE: MSELENI JOINT DISEASE

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 12 February 2016.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 28th February 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

pp Tubergen

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code of Federal Regulation Part 312.61 and 312.62.

Figure B5. Ethics approval from the University of Cape Town Human research ethics committee for survey data obtained by Gibbon in 2017.



May 6, 2013

Victoria Gibbon
Department of Anthropology
University of New Brunswick
UNBF - Campus Mail

Dear Dr. Gibbon:

RE: Mseleni Joint Disease, REB File # 2013-047

The above project is approved as modified.

Approval is valid for a period of three years from this date.

Annual Reports for this project are due on the 15th January of each year, provided that the date is at least six months after the date of project approval. **Final reports** are due 90 days after project completion. Both of these reports can be found on our website at <http://www.unb.ca/research/ors/forms/index.php#ethics>.

Although your application was processed via Expedited Review, for your information, we are providing a list of current Research Ethics Board members.

Sincerely,

R. Steven Turner, Chair
Research Ethics Board

REB Members:

- Maurice Gallant, Community Representative
- Barbara Burnett, Community Representative
- Jeff Landine, Faculty of Education
- Patricia Seaman, Faculty of Nursing
- Usha Kuruganti, Faculty of Kinesiology
- Jula Hughes, Faculty of Law (on Sabbatical Leave)
- Aloke Chatterjee, Faculty of Law (interim)
- R. Steven Turner (Chair), Faculty of Arts, Department of Psychology
- Renée Audet-Martel, REB Coordinator

Figure B6. Ethics approval from the University of University of New Brunswick Research Ethics Board for survey data obtained by Gibbon in 2013.

Appendix C. Consent forms and surveys



Project title:

Investigating the causes of Mseleni Joint Disease

| | |
|------------------------|---|
| Student Investigator | Elizabeth Dinkele , University of Cape Town, Department of Human Biology, Division of Clinical Anatomy and Biological Anthropology E-Mail: ptteli001@myuct.ac.za |
| Principal Investigator | Dr. Victoria Gibbon , University of Cape Town, Department of Human Biology, Division of Clinical Anatomy and Biological Anthropology, Observatory, Cape Town. E-Mail: Victoria.Gibbon@uct.ac.za Telephone: 021-406 4431 |
| Co-investigators | Dr. Robea Ballo , University of Cape Town, Department of Human Biology, Division of Cell Biology, Observatory, Cape Town. E-Mail: Robea.Ballo@uct.ac.za Telephone: 021-406 6036 Dr. Victor Fredlund , Mseleni Hospital, KwaZulu-Natal, South Africa. E-Mail: victor@mseleni.co.za . Telephone: 035 574 1004 |
| Human Ethics committee | Human Research Ethics Committee University of Cape Town E 52, Room 24, Old Main Building, Groote Schuur Hospital, Observatory. Telephone: 021 406 6492. Fax: 021 406 6411 |

Study information

Did you know, Mseleni Joint Disease (MJD) is a rare disease and only affects people living in this area? MJD causes joint and bone pain and many sufferers struggle to walk, work and do daily household tasks. Despite more than 40 years of research, the causes of this disease are still unknown.

The burden is felt by sufferers and their families. This research study seeks to identify the causes of MJD so that it can be prevented and treated to improve the lives of people living in this community.

To do this, we will analyse information from medical records at the Mseleni Hospital, but we will also ask questions to better understand the experiences of:

1. People who live in this region and have MJD.
2. People who live in this region and don't have MJD.
3. Doctors and nurses who treat MJD at the Mseleni Hospital.

We are inviting you to be part of the study, by answering questions about your life. You can choose whether or not you want to participate. If you choose to participate, you will need to agree by signing the consent form.

- **Purpose of this study**

To determine the cause of MJD we are collecting information from people who have the disease and those who don't, so we can understand what causes this disease. The information from your answers may help us find better ways to treat and prevent this disease and may improve the lives of those in your community with it.

- **Selection of participants**

We would like you to be part of this study if you are from the uMkhanyakude district and are older than 18 years. You have been asked to participate in this study because you are i) a member of this community and/or ii) you have Mseleni Joint Disease.

- **What do you have to do?**

Take 25 minutes to answer some questions about yourself and the community you live in. You will be asked questions in whichever language you prefer (Zulu or English), and your answers will be written down by Elizabeth Dinkele, one of the researchers in this study.

- **What type of questions will you be asked?**

You will be asked questions about your life (the food you eat, the place you live, the job you have etc.) and your experience of living in this area.

- **Will your answers be confidential?**

Yes, no information collected will be linked to you by name. This information will be kept at the University of Cape Town and at the end of this study, the information collected will be compiled into a Doctoral thesis by Mrs Elizabeth Dinkele. The research results will be published so that interested people may learn from our research.

- **Do you have to participate?**

No. Participation is voluntary. You can also withdraw at any point, without consequences.

- **Do you have any questions?**

Certificate of Consent:

I have understood this information and my questions have been answered and know I can ask Dr. Fredlund more questions later if I have them.

I agree to take part in this research.

Name and surname: _____

Signature/Fingerprint:

Date: _____



Participant Information

| | | | | |
|-----------------------|--|------------|-------------|---------------|
| Participant ID | | Sex | <i>Male</i> | <i>Female</i> |
| Date of birth | | MJD | <i>Yes</i> | <i>No</i> |
| Notes: | | | | |

Questions

| | | | | | | | |
|--|-----------------------------|----|-----------------------------------|--------------|--|--------------|---------------|
| Live in Mseleni | Yes | No | District | | | | |
| | | | How long? | < 5 years | 5-10 years | 10-20 years | <20 years |
| Born in Mseleni | Yes | No | District | | | | |
| Grown up in Mseleni | Yes | No | District | | | | |
| Parents born in Mseleni | Yes | | | | No | Unknown | |
| | Mother | | Father | | | | |
| | District | | District | | | | |
| Home type | | | | | | | |
| Present | Hut (mud, sticks, branches) | | Shack (corrugated sheeting, wood) | | Concrete structure (concrete, bricks, windows) | | Other |
| How long? | < 5 years | | 5-10 years | | 10-20 years | | >20 years |
| Past | Hut (mud, sticks, branches) | | Shack (corrugated sheeting, wood) | | Concrete structure (concrete, bricks, windows) | | Other |
| How long? | < 5 years | | 5-10 years | | 10-20 years | | >20 years |
| Reason for change in housing? | Marriage | | Government housing | Job location | | Unemployment | Better salary |
| | Other | | | | | | |
| Average number of meals per day | | | | | | | |
| Primary food source | | | | | | | |

| | | | | | |
|--------------------------------------|------------------------------------|------------------|-----------------------------|------------------------|----------------|
| Present | Spar/Boxer superstore/ Shoprite | Spaza shop | Farm own/communit y land | Gathering/ Foraging | Other |
| How long? | < 5 years | 5-10 years | 10-20 years | >20 years | |
| Past | Spar/Boxer superstore/ Shoprite | Spaza shop | Own/ community land | Other | |
| How long? | < 5 years | 5-10 years | 10-20 years | >20 years | |
| Regular diet | | | | | |
| Present | Beans | Samp | Pap/Maize meal | Potatoes | |
| | Pine nuts | Rice | Beer | Sorghum | |
| | Milk | Beef | Chicken | Lamb | |
| How long? | Goat | Vegetables | | | |
| < 5 years | 5-10 years | 10-20 years | <20 years | Other | |
| Past | Beans | Samp | Pap/Maize meal | Potatoes | |
| | Pine nuts | Rice | Beer | Sorghum | |
| | Milk | Beef | Chicken | Lamb | |
| How long? | Goat | Vegetables | | | |
| < 5 years | 5-10 years | 10-20 years | <20 years | Other | |
| Reason for change in diet? | Marriage | Age | Better salary | Unemployment | |
| | Other | | | | |
| Do you have electricity? | | | | | |
| Cooking method | | | | | |
| Present | Fire | Paraffin stove | Electric stove | Other | |
| How long? | | | | | |
| < 5 years | 5-10 years | 10-20 years | <20 years | | |
| Past | Fire | Paraffin stove | Electric stove | Other | |
| How long? | | | | | |
| < 5 years | 5-10 years | 10-20 years | <20 years | | |
| Reason for change in cooking method? | Marriage | Age | Better salary | Unemployme nt | Housing change |
| | Electricity | Other | | | |
| Water source | | | | | |
| Present | Household tap | Community tap | Well | Reservoir | Other |
| How long? | < 5 years | 5-10 years | 10 -20 years | >20 years | |
| Past | Household tap | Community tap | Well | Reservoir | Other |
| How long? | < 5 years | 5-10 years | 10 -20 years | >20 years | |
| Reason for change in water source? | Marriage | New house | Government development | Better salary | |
| | Electricity | Other | | | |
| Water carried far distances | | | | | |

| | | | | | | | |
|--|--------------------------|-----------------------------|----------------------------------|--------------------------|-----------------|-----------------|--|
| Present | Yes | No | | | | | |
| If yes, how? | In a vehicle | Carried on head | Family help | By hand | Other | | |
| How long? | < 5 years | 5-10 years | 10-20 years | | >20 years | | |
| Number of times water is collected in per week (if collected by you)? | NA | Less than once a week | Once a week | More than 3 times a week | Daily | | |
| Past | Yes | No | | | | | |
| If yes, how? | Carried on head | Family help | By hand | Other | | | |
| How long? | < 5 years | 5-10 years | 10-20 years | | >20 years | | |
| Number of times water was collected in per week (if collected by you)? | NA | Less than once a week | Once a week | More than 3 times a week | Daily | | |
| Storage of water | Yes | No | | | | | |
| In what? | Steel tin/drum or bucket | Iron pot | Plastic bottle/ container/bucket | | Other | | |
| Where? | Inside house | Outside house | In Fridge | | Other | | |
| How long? | <3 days | 3-7 days | | > 7 days | | | |
| Primary mode of transport | | | | | | | |
| Present | Walking | Car | Taxi | Bus | Bicycle | Other | |
| How long? | < 5 years | 5-10 years | 10 -20 years | | >20 years | | |
| Past | Walking | Car | Taxi | Bus | Bicycle | Other | |
| How long? | < 5 years | 5-10 years | 10-20 years | | >20 years | | |
| Job/employment | | | | | | | |
| Present | | | | | | | |
| How long? | < 5 years | 5-10 years | 10 -20 years | | >20 years | | |
| Past | | | | | | | |
| How long? | < 5 years | 5-10 years | 10 -20 years | | >20 years | | |
| Do you smoke or chew tobacco? | Yes | | | No | | | |
| What? | Pipe | <i>Cigarettes</i> | | | Chew | Other | |
| | | Self-rolled (filter) | Self-rolled (no filter) | Purchased | | | |
| How often? | Unsure | Special occasions/ socially | Once a week | 1-3 times a day | 3-8 times a day | > 8 times a day | |
| Do you drink alcohol | Yes | | | No | | | |
| What? | Beer (homemade) | Beer (store-bought) | Ciders | Hard liquor | Other | | |
| When | Daily | Weekly | Monthly/celebrations | | Other | | |

| | | | | | |
|--|------------|-------------|--------------|----------|-------------------|
| Have you ever heard of MJD? | | | | | |
| Does anyone in your family have MJD? <i>For how long?</i> -5: less than 5 years ~ 10: 5 to 10 years ~ 20: 10- 20 years +20: more than 20 years ***M/F: mother/fathers' side | Yes | | No | | |
| | Wife | Mother | Sister | Daughter | Grandfather (M/F) |
| | Husband | Father | Brother | Son | Grandmother (M/F) |
| | Aunt (M/F) | Uncle (M/F) | Cousin (M/F) | Other | |
| Do you have bone or joint pain? | Yes | | No | | |
| Are you here today because of joint pain? | Yes | | No | | |

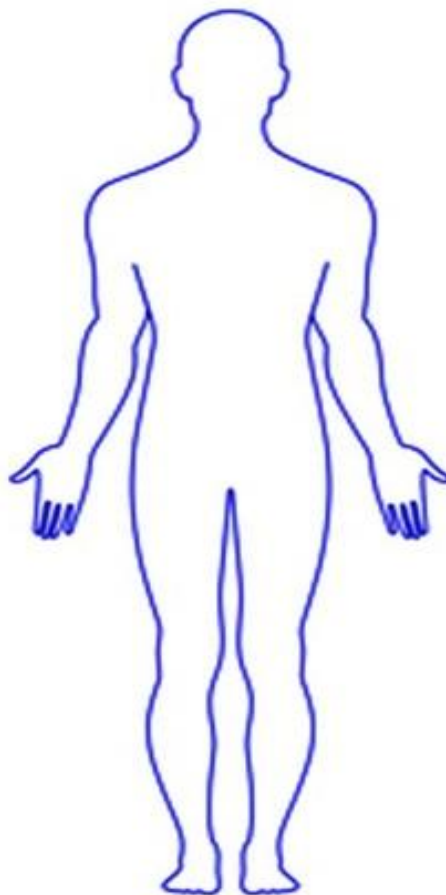


Figure C1. Informed consent forms and semi-structured surveys used for Mseleni community members.



Project title: **Investigating the causes of Mseleni Joint Disease**

| | |
|------------------------|--|
| Student Investigator | Elizabeth Dinkele , University of Cape Town, Department of Human Biology, Division of Clinical Anatomy and Biological Anthropology E-Mail: ptteli001@myuct.ac.za |
| Principal Investigator | Assoc Prof Victoria Gibbon , University of Cape Town, Department of Human Biology, Division of Clinical Anatomy and Biological Anthropology, Observatory, Cape Town. E-Mail: Victoria.Gibbon@uct.ac.za Telephone: 021-406 4431 |
| Co-investigators | Dr. Robea Ballo , University of Cape Town, Department of Human Biology, Division of Cell Biology/Nutrition/Physiology, Observatory, Cape Town. E-Mail: Robea.Ballo@uct.ac.za Dr. Victor Fredlund , Mseleni Hospital, KwaZulu-Natal, South Africa. E-Mail: victor@mseleni.co.za . Telephone: 035 574 1004 |
| Human Ethics committee | Human Research Ethics Committee University of Cape Town E 52, Room 24, Old Main Building, Groote Schuur Hospital, Observatory. Telephone: 021 406 6492. Fax: 021 406 6411 |

Study information

Did you know, Mseleni Joint Disease (MJD) is a rare disease and only affects people living in this area? MJD causes joint and bone pain and many sufferers struggle to walk, work and do daily household tasks. Despite more than 40 years of research, the causes of this disease are still unknown.

The burden of this disease is felt by sufferers and their families. This research study seeks to identify the causes of MJD so that it can be prevented or treated to improve the lives of people living in this community.

To do this, we will be getting information from medical records at the Mseleni Hospital, but we will be asking questions to better understand the experiences of:

4. People who live in this region and have MJD
5. People who live in this region and don't have MJD
6. Doctors and nurses who treat MJD at the Mseleni Hospital

We are inviting you to be part of the research study, by answering questions about your life. You can choose whether or not you want to participate. If you are going to participate in the research, you will have to agree by giving your consent and signing the consent form. If you do not wish to take part in the research, you do not have to and there will be no consequences

- **Purpose of this study**

To determine the cause of Mseleni Joint Disease. We are collecting information from people who have MJD and people without this disease, so we can understand what causes MJD. The information from your answers may help us find better ways to treat and prevent this disease and may improve the lives of those in your community with it.

- **Selection of participants**

We would like you to be part of this study if you are from the uMkhanyakude district and are older than 18 years. You have been asked to participate in this study because you are i) a member of this community and/or ii) you have Mseleni Joint Disease.

- **What do you have to do?**

Take 40 minutes to answer some questions about yourself and the community you live in. You will be asked questions in whichever language you prefer (Zulu or English), and voice recordings of your answers will be taken by Elizabeth Dinkele, one of the researchers in this study.

- **What type of questions will you be asked?**

You will be asked questions about your life (the food you eat, the place you live, the job you have etc.) and your experience of living in this region.

- **Will your answers be confidential?**

Yes, none of the information collected will be linked to you by name. This information will be kept at the University of Cape Town and at the end of this research study, the information collected will be compiled into a Doctoral thesis by Mrs Elizabeth Dinkele. The research results will be published so that interested people may learn from our research.

- **Do you have to participate?**

No. Participation is voluntary. You can also withdraw at any point, without consequences.

- **Do you have any questions?**

Certificate of Consent:

I have understood this information and my questions have been answered and know I can ask Dr. Fredlund more questions later if I have them.

I agree to take part in this research.

Name and surname: _____

Signature/Fingerprint:

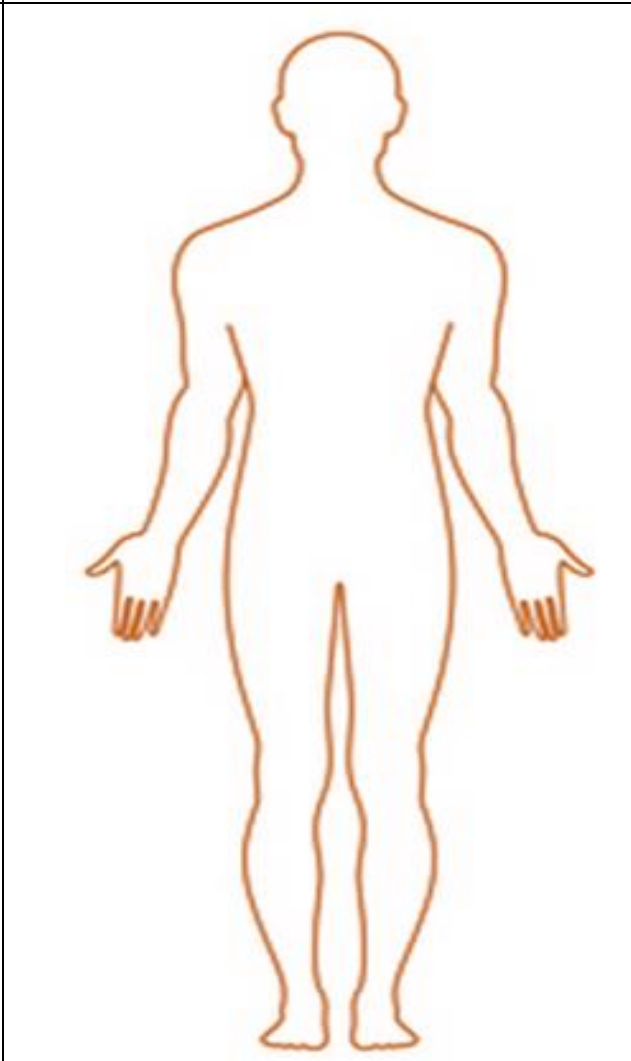
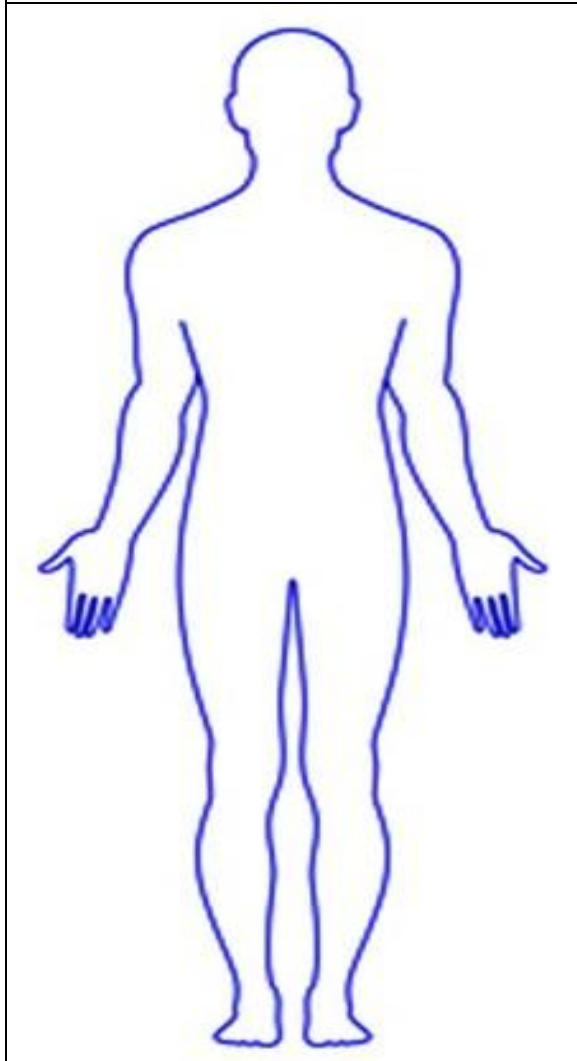
Date: _____



Project title: Investigating the causes of Mseleni Joint Disease

| Participant Information | | | | |
|-------------------------|--|------------------------|----------|----------|
| Participant ID | | Sex | Male | Female |
| Date of birth | | Mseleni Joint Disease | Positive | Negative |
| Additional notes | | Dwarfism (MJD-related) | Positive | Negative |

| Questions | | | | |
|--|--|------------|--------------|-----------|
| What age were you diagnosed with MJD? | | | | |
| When did you first experience pain? | < 5 years | 5-10 years | 10 -20 years | >20 years |
| Where did you first experience pain? Timing of onset (1-5) | Where do you experience pain now ? Timing of onset (1-5) | | | |



| | | | | | | |
|---|--------------------------------------|-------------|--|------------------------|------------------------------|-------|
| When did you first hear about MJD in your community? | < 5 years | 5-10 years | 10 -20 years | 20-30 years | >30 years | |
| How has MJD impacted your life? | | | | | | |
| How has MJD affected your movement? | No change in mobility | | Walking with difficulty, no stick required | | Walking with a stick/support | |
| | Limited movement but can walk | | Cannot walk, need help to move. | | Other | |
| Does anyone else in your family have MJD? (Number of people- 1,2, etc) (Yes-Tick; No-Cross; Unknown-Question mark) | Father | Mother | Sister | Brother | Aunt | Uncle |
| | Husband | Wife | Daughter | Son | Other | |
| When is the pain you experience the worst? | Morning | Evening | All day | Unsure | Other | |
| Which best describes your pain? | No pain | | | Pain in joints only | | |
| Are you on any medicine for MJD? | | | | | | |
| Has someone worked with your joints and muscles to help movement? | | | | | | |
| Have you had any surgery for MJD? | Yes | | | | No | |
| | Age | | | | | |
| | Joint/s: | Hip (L/R/B) | Knee (L/R/B) | Shoulders/arms (L/R/B) | Back/Neck (U/M/L) | |
| | Do you still feel pain in that area? | | | | | |
| What do you think causes MJD? | | | | | | |

Figure C2. Informed consent forms and semi-structured surveys used for interviews with MJD patients.



Project title:
Investigating the causes of Mseleni Joint Disease

Student Investigator **Elizabeth Dinkele**, University of Cape Town, Department of Human Biology, Division of Clinical Anatomy and Biological Anthropology
E-Mail: ptteli001@myuct.ac.za

Principal Investigator **Assoc Prof Victoria Gibbon**, University of Cape Town, Department of Human Biology, Division of Clinical Anatomy and Biological Anthropology, Observatory, Cape Town.
E-Mail: Victoria.Gibbon@uct.ac.za Telephone: 021-406 4431

Co-investigators **Dr. Robea Ballo**, University of Cape Town, Department of Human Biology, Division of Cell Biology/Nutrition/Physiology, Observatory, Cape Town.
E-Mail: Robea.Ballo@uct.ac.za

Dr. Victor Fredlund, Mseleni Hospital, KwaZulu-Natal, South Africa.
E-Mail: victor@mseleni.co.za. Telephone: 035 574 1004

Human Ethics committee **Human Research Ethics Committee**
University of Cape Town
E 52, Room 24, Old Main Building, Groote Schuur Hospital, Observatory. Telephone: 021 406 6492. Fax: 021 406 6411

Study information

You are invited to participate in a study on Mseleni Joint Disease because of your experience as a nurse in this region. As you know, MJD is rare and only affects people living in this area. Despite more than 40 years of research, the causes of this disease are still unknown.

The burden of this disease is felt by sufferers, their families and the healthcare system in this region. This research study seeks to identify factors associated with aetiology of MJD so that this disease can be prevented, treated and managed more effectively.

To do this, we will be analysing data from medical records at the Mseleni Hospital, to evaluate the demographic distribution and prevalence of MJD. We will also be asking questions to better understand the experiences of:

1. People who live in this region and have MJD
2. People who live in this region and don't have MJD
3. Doctors and nurses who treat MJD at the Mseleni Hospital

We are inviting you to be part of the research study, by answering questions about your experience of MJD at this hospital.

- **Purpose of this study**

To understand the aetiology of MJD. We are hoping that your experience of caring for patients with this disease may provide us with some knowledge and insight we can use to identify factors causing MJD. Information from your answers may help us find better ways to treat and prevent this disease and may improve the lives of those in your community living with it.

- **What do you have to do?**

Take 25 minutes to answer some questions about your experience caring for patients with this disease. You will be asked questions by a researcher (Elizabeth Dinkele) who will document and take voice recordings of your answers.

- **What type of questions will you be asked?**

You will be asked questions about your qualifications, position at the hospital and experience of MJD in the community (pattern of morbidity, number of patients seen etc.)

- **Can you still participate if you haven't cared for any patients with MJD?**

Yes. Your experience as nurse at the hospital and a member of this community will give us an indication of the burden of this disease in the region.

- **Will your answers be confidential?**

Yes, none of the information collected will be linked to you by name. This information will be kept at the University of Cape Town and at the end of this research study, the information collected will be compiled into a Doctoral thesis by Mrs Elizabeth Dinkele. The research results will be published so that interested people may learn from our research.

- **Do you have to participate?**

No. Participation is voluntary, and you can withdraw at any point without consequences.

- **Do you have any questions?**

Certificate of Consent:

I have understood this information and my questions have been answered and know I can ask more questions to Dr. Fredlund later if I have them.

I agree to take part in this research.

Name and surname: _____

Signature:

Date: _____



Project title:
**Investigating the causes of
 Mseleni Joint Disease**

| Participant Information | | | | | | |
|--|--------------------|---------------|----------------|--------------------------------|-------------|-------|
| Participant number | | | | Sex | | |
| DOB | | | | Home language | | |
| Years of experience | | | | Where are you originally from? | | |
| Qualifications | | | | Where did you study? | | |
| At which hospitals/clinics have you worked or trained? | | | | | | |
| Position in the hospital | Professional nurse | Trainee nurse | Neonatal nurse | Paediatric nurse | Ward sister | Other |

| Questions | | | | | | |
|--|------------|-------------|-------------|-------------|-----|----------|
| How long have you been working at the Mseleni Provincial Hospital? | <1 year | 1-3 years | 3-5 years | >5 years | | |
| What ward do you work in/ what is your speciality in the hospital? | | | | | | |
| Had you heard of Mseleni Joint Disease prior to working at this hospital? | Yes | No | Details | | | |
| How many patients with MJD have you cared for in your time at this hospital? | 0 | 1-5 | 5-10 | 10-30 | >30 | |
| The following pertain to patients who seek medical intervention for MJD | | | | | | |
| In your experience, in what age range do MJD patients fall? | < 10 years | 10-18 years | 20-40 years | 40-60 years | > | 60 years |

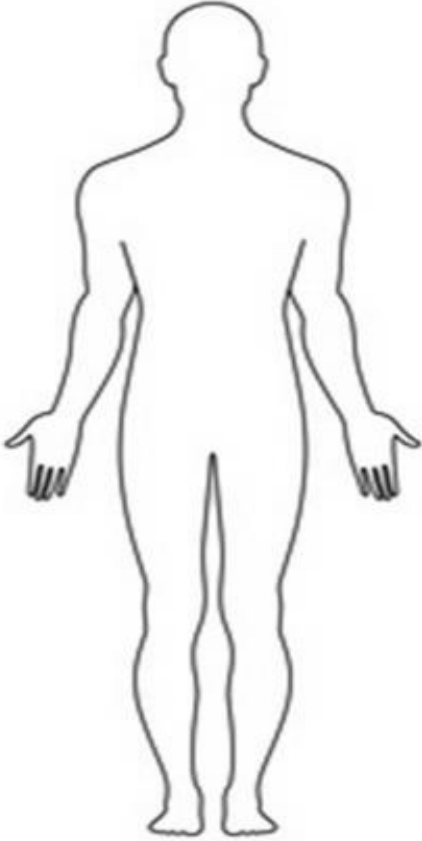
| | | | | |
|---|---|------------|--------------------|-------|
| <p>In what regions of the body to patients normally report pain?</p> |  | | | |
| <p>What is the greatest complaint of patients with MJD?</p> | Pain | Immobility | Standard living of | Other |
| <p>What do you think the causes MJD?</p> | | | | |
| <p>Are there any factors that stop people with MJD from visiting the clinic or hospital?</p> | | | | |
| <p>How does this disease impact sufferers and the community?</p> | | | | |
| <p>How do you think treatment of MJD could be improved?</p> | | | | |

Figure C3. Informed consent forms and semi-structured surveys used for interviews with nurses at the Mseleni Hospital.



Project title: **Investigating the causes of Mseleni Joint Disease**

| | |
|------------------------|--|
| Student Investigator | Elizabeth Dinkele , University of Cape Town, Department of Human Biology, Division of Clinical Anatomy and Biological Anthropology E-Mail: ptteli001@myuct.ac.za |
| Principal Investigator | Assoc Prof Victoria Gibbon , University of Cape Town, Department of Human Biology, Division of Clinical Anatomy and Biological Anthropology, Observatory, Cape Town. E-Mail: Victoria.Gibbon@uct.ac.za Telephone: 021-406 4431 |
| Co-investigators: | Dr. Robea Ballo , University of Cape Town, Department of Human Biology, Division of Cell Biology/Nutrition/Physiology, Observatory, Cape Town. E-Mail: Robea.Ballo@uct.ac.za Dr. Victor Fredlund , Mseleni Hospital, KwaZulu-Natal, South Africa. E-Mail: victor@mseleni.co.za . Telephone: 035 574 1004 |
| Human Ethics committee | Human Research Ethics Committee University of Cape Town E 52, Room 24, Old Main Building, Groote Schuur Hospital, Observatory. Telephone: 021 406 6492. Fax: 021 406 6411 |

Study information

You are invited to participate in a study on Mseleni Joint Disease because of your experience as a doctor in this region. As you know, MJD is rare and only affects people living in this area. Despite more than 40 years of research, the causes of this disease are unknown.

The burden of this disease is felt by sufferers, their families and the healthcare system in this region. This research study seeks to identify factors associated with aetiology of MJD so that this disease can be prevented, treated and managed more effectively.

To do this, we will be analysing data from medical records at the Mseleni Hospital, to evaluate the demographic distribution and prevalence of MJD. We will also be asking questions to better understand the experiences of:

1. People who live in this region and have MJD
2. People who live in this region and don't have MJD
3. Doctors and nurses who treat MJD at the Mseleni Hospital

We are inviting you to be part of the research study, by answering questions about your life. You can choose whether or not you want to participate. If you are going to participate in the research, you will have to agree by giving your consent and signing the consent form. If you do not wish to take part in the research, you do not have to and there will be no consequences

- **Purpose of this study**

To understand the aetiology of MJD. We are hoping that your experience of treating patients with disease may provide us with some knowledge and insight we can use to identify factors implicated in its aetiology. Information from your answers may help us find better ways to treat and prevent this disease and may improve the lives of those in your community living with it.

- **What do you have to do?**

Take 40 minutes to answer some questions about your experience treating patients with this disease. You will be asked questions by a researcher (Elizabeth Dinkele) who will take voice recordings of your answers.

- **What type of questions will you be asked?**

You will be asked questions about your qualifications, position at the hospital and experience of MJD in the community (pattern of morbidity, number of patients seen etc.)

- **Can you still participate if you haven't treated any patients who have MJD?**

Yes. Your experience as doctor at the Mseleni hospital will give us an indication of the burden of this disease on the health system in this region.

- **Will your answers be confidential?**

Yes, none of the information collected will be linked to you by name. This information will be kept at the University of Cape Town and at the end of this research study, the information collected will be compiled into a Doctoral thesis by Mrs Elizabeth Dinkele. The research results will be published so that interested people may learn from our research.

- **Do you have to participate?**

No. Participation is voluntary. You can also withdraw at any point, without consequences.

- **Do you have any questions?**

Certificate of Consent:

I have understood this information and my questions have been answered and know I can ask Dr. Fredlund more questions later if I have them.

I agree to take part in this research.

Name and surname: _____

Signature:

Date: _____



Project title: Investigating the causes of Mseleni Joint Disease

| Participant Information | | | | | | |
|--------------------------|--------------------------|-------------------|----------|--------------------------------|------------|--------|
| Participant number | | | | Sex | Male | Female |
| Date of Birth | | | | Home language | | |
| Years of experience | | | | Where are you originally from? | | |
| Qualifications | | | | Where did you train? | | |
| Position in the hospital | Community service doctor | Internship doctor | Resident | Senior doctor | Specialist | Other |

| Questions | | | | | | |
|--|------------|-------------|-------------|-------------|------------|--|
| How long have you been working at the Mseleni Provincial Hospital? | | | | | | |
| What is your speciality/role at this hospital? | | | | | | |
| Had you heard of Mseleni Joint Disease prior to working at this hospital? | Yes | No | Details | | | |
| How many patients that had MJD have you treated in your field? | 0 | 1-5 | 5-10 | 10-30 | >30 | |
| <i>The following questions pertain to patients who seek medical intervention for MJD</i> | | | | | | |
| In your experience, in what age range do MJD patients fall? | < 10 years | 10-18 years | 20-40 years | 40-60 years | > 60 years | |
| In what age group is MJD most prevalence? | | | | | | |
| Does this disease affect males and females equally? | Yes | No | Details | | | |
| At what age do patients initially report feeling pain? | < 10 years | 10-18 years | 20-40 years | 40-60 years | > 60 years | |
| At what age do patients seek medical intervention for MJD? | < 10 years | 10-18 years | 20-40 years | 40-60 years | > 60 years | |

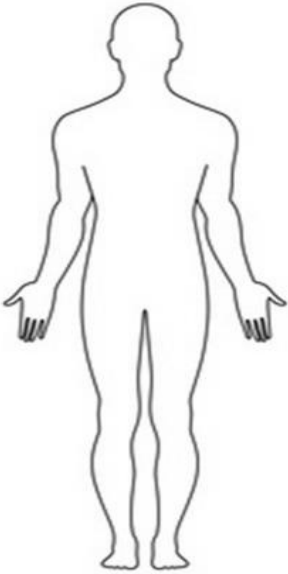
| | | | | |
|---|---|----------|------|-------|
| Where do consultations with MJD patients mainly occur? | Clinic | Hospital | Home | Other |
| Have you encountered more patients with MJD at the clinics or Mseleni hospital? | | | | |
| What criteria and tests are used to diagnose MJD? | | | | |
| In what regions of the body to patients normally report pain? |  | | | |
| What treatment is prescribed for patients with limited joint movement? | | | | |
| What treatment is prescribed for patients with severe immobility? | | | | |
| What factors contribute to the progression of MJD? | | | | |
| Do you think there are any factors which may stop people from seeking help for MJD? | | | | |
| Do you think there are anyways the treatment of MJD could be improved? Are there any barriers to these improvements? | | | | |
| How does this disease impact sufferers and the community? | | | | |
| What do you think causes MJD? | | | | |

Figure C4. Informed consent forms and semi-structured surveys used for interviews with doctors at the Mseleni Hospital.

Appendix D. Supplementary tables

Table D1. Frequency distribution of joint pain reported by patients with Mseleni joint disease in surveys from 2013 and 2017.

| | Upper limb | | | | | | Lower limb | | | | | | Vertebrae | |
|-----------|------------|----|----------|----|------------------|----|------------|----|----------|----|-----------------|----|------------------------------|----|
| | Shoulders | | Elbows | | Wrists/ hands | | Hips | | Knees | | Ankles/ feet | | Lumbar spine [†] | |
| | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % |
| Right | 13 | 43 | 12 | 40 | 3 | 10 | 27 | 90 | 20 | 67 | 10 | 33 | - | - |
| Left | 11 | 37 | 10 | 33 | 1 | 3 | 27 | 90 | 18 | 60 | 9 | 30 | - | - |
| Bilateral | 11 | 37 | 10 | 33 | 12 | 40 | 27 | 90 | 18 | 60 | 8 | 27 | 9 | 30 |

Abbreviations/symbols: n-number of individuals; %-percentage. All percentages were calculated using the total participants from surveys in 2013 and 2017, n = 30.

[†] Sidedness was not assessed, and all lumbar spine pathology was listed as bilateral.

Table D2. Frequency of responses about of age/time of onset, family history of Mseleni joint disease (MJD) and treatment from surveys of patients with MJD from 2013 and 2017.

| Topic | Categories | <i>n</i> | % |
|-------------------------|------------------------------------|-------------------|----|
| Onset age | Childhood/Adolescence [†] | 5 | 16 |
| | 19-29 years | 4 | 13 |
| | 30-49 years | 11 | 35 |
| | 50-69 years | 4 | 13 |
| | No response | 7 | 23 |
| | Total | 31 | |
| | Family history [‡] | One family member | 6 |
| Multiple family members | | 9 | 47 |
| None | | 4 | 21 |
| Total | | 19 | |
| Treatment history | Analgesia only | 16 | 52 |
| | Joint arthroplasty | 10 | 32 |
| | No response | 5 | 16 |
| | Total | 31 | |

Abbreviations/symbols: n-number of individuals; %-percentage.

[†] Onset age was listed as childhood or teenage years by the patient and no specific age was given.

[‡] Family history of MJD was only assessed in 2017.

Table D3. Reasons for patient visits to the outpatients department at the Mseleni Hospital in May 2019.

| | MJD positive (n = 66) | | MJD negative (n = 657) | | Total sample (n=723) | |
|---|----------------------------------|----------|-----------------------------------|----------|---------------------------------|----------|
| | <i>n</i> | <i>%</i> | <i>n</i> | <i>%</i> | <i>n</i> | <i>%</i> |
| Reasons for visits by body systems | | | | | | |
| Rheumatology | 26 | 39 | 40 | 61 | 66 | 9 |
| Neurology | 1 | 6 | 15 | 94 | 16 | 2 |
| Dental | 0 | 0 | 69 | 100 | 69 | 10 |
| Ear, nose and throat | 0 | 0 | 40 | 100 | 40 | 6 |
| Pulmonary | 2 | 3 | 62 | 97 | 64 | 9 |
| Cardiovascular | 0 | 0 | 13 | 100 | 13 | 2 |
| Gastrointestinal tract | 0 | 0 | 43 | 100 | 43 | 6 |
| Urology, renal or hepatic | 2 | 4 | 52 | 96 | 54 | 7 |
| Gynaecology/obstetrics | 1 | 2 | 41 | 98 | 42 | 6 |
| Trauma/Emergency admission | 4 | 5 | 78 | 95 | 82 | 11 |
| Tests and prescription refills | | | | | | |
| Diagnostic tests | 1 | 2 | 49 | 98 | 50 | 7 |
| Prescription renewal | 9 | 21 | 33 | 79 | 42 | 6 |
| Pre-booked appointments | | | | | | |
| MJD clinic | 17 | 85 | 3 | 15 | 20 | 3 |
| Occupational/physiotherapy | 1 | 11 | 8 | 89 | 9 | 1 |
| Psychology | 1 | 4 | 26 | 96 | 27 | 4 |
| No record | 1 | 1 | 85 | 99 | 86 | 12 |
| Total sample | 66 | | 657 | | 723 | |

*Abbreviations/symbols: n-number of individuals; % - percentage; MJD- Mseleni Joint Disease
Percentages calculated within rows.*

Table D4. Distribution according to sex for different age groups affected by Mseleni Joint Disease from medical record reviews.

| Literature identified from PubMed, Medline, EMBASE databases | | | |
|---|--|-------------|---|
| | Article title | Year | Authors |
| 1 | High prevalence of hepatitis B virus infection in rural black adults in Mseleni, South Africa | 1989 | Abdool Karim SS, Thejpal R, Singh B |
| 2 | OA. | 1995 | Adebajo AO. |
| 3 | Mseleni and Handigodu familial osteoarthropathies: syndromic identity | 1997 | Agarwal SS, Phadke SR, Fredlund V, Viljoen D, Beighton P. |
| 4 | Consult Online: digital advice for tropical doctors | 2012 | Baerends EP, Reuling EM, Bijen CB |
| 5 | Mseleni joint disease--a molecular genetic approach to defining the aetiology. | 1996 | Ballo R, Viljoen D, Machado M, Keene D, Horton W, Fredlund V, Jacobs M, Martell R, Beighton P, Ramesar R. |
| 6 | Mseleni joint disease progress | 2000 | Bateman C |
| 7 | A case of dilated cardiomyopathy | 2012 | Binham JD, Fredlund V. |
| 8 | Unusual Urine Color During Catheterization | 2016 | Burg MD, Baerends EP, Hendrik Bell C. |
| 9 | Mseleni joint disease: biochemical survey. | 1973 | Burger FJ, Elphinstone CD, Fellingham SA, Grey PC, Hogewind ZA. |
| 10 | Hip disease of Mseleni. | 1979 | Du Toit GT |
| 11 | Mseleni joint disease: background and prevalence. | 1973 | Fellingham SA, Elphinstone CD, Wittmann W. |
| 12 | Mseleni joint disease. | 1986 | Fincham |
| 13 | Mseleni joint disease. Part I. An animal model? | 1985 | Fincham JE, Hough FS, Taljaard JJ, Capatos D. |
| 14 | Mseleni joint disease. Part II. Low serum calcium and magnesium levels in women. | 1986 | Fincham JE, Hough FS, Taljaard JJ, Weidemann A, Schutte CH |
| 15 | Serum alkaline phosphatase levels in rural blacks living near Mseleni. | 1985 | Fincham JE, Schutte CH. |
| 16 | Mseleni joint disease--a manganese deficiency? | 1981 | Fincham JE, van Rensburg SJ, Marasas WF |
| 17 | Six-month intermittent chemotherapy for tuberculosis in the Mseleni Health Ward of KwaZulu. | 1990 | Fredlund VG |
| 18 | How far should they walk? Increasing antiretroviral therapy access in a rural community in northern KwaZulu-Natal, South Africa. | 2007 | Fredlund VG, Nash J. |
| 19 | Mseleni joint disease: a potential model of epigenetic chondrodysplasia | 2010 | Gibbon VE, Harington JS, Penny CB, Fredlund V. |
| 20 | Falciparum malaria: a case report of severe hyponatraemia. | 2000 | Hartung TK, Fredlund VG |
| 21 | Suspected pulmonary tuberculosis in rural South Africa--sputum induction as a simple diagnostic tool? | 2002 | Hartung TK, Maulu A, Nash J, Fredlund VG |
| 22 | AIDS awareness and sexual behaviour in a high HIV prevalence area in rural northern Kwazulu-Natal, South Africa. | 2002 | Hartung TK, Nash J, Ngubane N, Fredlund VG |
| 23 | Regression with an ordered categorical response | 1989 | Hastie TJ, Botha JL, Schnitzler CM. |
| 24 | The practice of traditional birth attendants in Zululand. | 1988 | Jepson AP, MacDonald LD |
| 25 | Mseleni joint disease: a radiological study of two affected families. | 1973 | Lockitch G, Fellingham SA, Elphinstone CD |
| 26 | Mseleni joint disease: the pilot clinical survey. | 1973 | Lockitch G, Fellingham SA, Wittman W, de Villiers PD, de Wet IS, du Toit GT. |
| 27 | Mseleni joint disease: food and water supplies. | 1973 | Lubbe AM, Elphinstone CD, Fellingham SA. |
| 28 | Something fishy about Mseleni joint disease. | 1981 | Mackenzie DB. |

| | | | |
|--|---|------|--|
| 29 | Mycotoxycological investigations on maize and groundnuts from the endemic area of Mseleni joint disease in Kwazulu. | 1986 | Marasas WF, Van Rensburg SJ. |
| 30 | Double-blind placebo-controlled trial of Mycobacterium vaccae immunotherapy for tuberculosis in KwaZulu, South Africa, 1991-97 | 2000 | Mayo RE, Stanford JL |
| 31 | Mseleni joint disease: not a borreliosis. | 1977 | McGlashan ND, Frean JA, Harington JS, McGlashan HI, Larsen SA.. |
| 32 | Prevalence of motor impairment and disability in a rural community in KwaZulu | 1987 | McLaren PA, Gear JS, Irwig LM, Smit AE. |
| 33 | A rural perspective: four stories | 2012 | Nash J, Rapatsa A, Reid S, Gaunt B |
| 34 | Slow virus in Mseleni joint disease. | 1985 | Nurse GT. |
| 35 | Histomorphometric analysis of osteopenia associated with endemic OA (Mseleni joint disease) | 1988 | Schnitzler CM, Pieczkowski WM, Fredlund V, Mesquita JM, Sweet MB, Smit AE. |
| 36 | Osteopenia of the pelvis associated with Mseleni joint disease. Radiological aspects. | 1987 | Schnitzler CM, Solomon L, Botha JL, McLaren P. |
| 37 | Clinical case of the late diagnosis of type-II schizencephaly. | 2007 | Sitnikov AR |
| 38 | Early infant diagnosis of HIV and fast initiation of anti-retroviral therapy in a rural African setting: how well are we doing? | 2014 | Smith SJ, Nimmo C, Fredlund V, Moodley P. |
| 39 | Pathologic features of the femoral head in Mseleni disease. | 1985 | Sokoloff L, Fincham JE, du Toit GT. |
| 40 | Distinct types of hip disorder in Mseleni joint disease. | 1981 | Solomon L, McLaren P, Irwig L, Gear JS, Schnitzler CM, Gear A, Mann D. |
| 41 | Proteoglycans of articular cartilage in Mseleni joint disease. | 1987 | Sweet MB, Schnitzler CM, Hough FS. |
| 42 | Caring for the caregivers: models of HIV/AIDS care and treatment provision for health care workers in Southern Africa. | 2007 | Uebel KE, Nash J, Avalos A. |
| 43 | Brachydactylous dwarfs of Mseleni. | 1993 | Viljoen D, Fredlund V, Ramesar R, Beighton P. |
| 44 | Mseleni Joint Disease: social priorities. | 1998 | Waller RM. |
| 45 | Mseleni joint disease in 1981: decreased prevalence rates, wider geographical location than before, and socioeconomic impact of an endemic osteoarthritis in an underdeveloped community in South Africa. | 1985 | Yach D, Botha JL. |
| 46 | Mseleni disease serum is not harmful to cultured chondrocytes. | 1987 | Changlong Yu, Fincham JE, Wright GC Jr, Taljaard JJ, Sokoloff L |
| Articles identified from reference checking | | | |
| 47 | Aspects of the social effects of Mseleni joint disease | 1984 | Mann |
| 48 | A study of the clinical and radiological aspects including possible modes of inheritance | 1974 | Lockitch |
| 49 | Unusual hip disease in remote part of Zululand | 1970 | Wittman and Fellingham |
| 50 | Mseleni Joint Disease: Population Genetics Studies | 1974 | Nurse GT and Jenkins T |
| 51 | The social impact of Mseleni Joint Disease | 1988 | Mann & Fredlund |

Table D5. Distribution according to sex for different age groups affected by Mseleni Joint Disease from the medical record review.

| Variables | Women (n = 446) | | Men (n = 277) | | Total sample (n=723) |
|-------------------------------------|--------------------|-----------------|------------------|-----------------|-------------------------|
| | MJD positive | MJD negative | MJD positive | MJD negative | |
| | n (%) | n (%) | n (%) | n (%) | |
| Age categories [‡] [years] | | | | | |
| 6-10 | 0 (0) | 8 (100) | 0 (0) | 10 (100) | 18 (3) |
| 11-20 | 0 (0) | 33 (100) | 0 (0) | 39 (100) | 72 (10) |
| 21-30 | 0 (0) | 75 (100) | 0 (0) | 40 (100) | 115 (16) |
| 31-40 | 0 (0) | 79 (100) | 1 (2) | 45 (98) | 125 (17) |
| 41-50 | 7 (9) | 71 (91) | 1 (3) | 36 (97) | 115 (16) |
| 51-60 | 17 (20) | 69 (80) | 4 (13) | 27 (87) | 117 (16) |
| 61-70 | 7 (19) | 30 (81) | 7 (18) | 31 (82) | 75 (10) |
| 71+ | 18 (36) | 32 (64) | 4 (11) | 32 (89) | 86 (12) |

Abbreviations/symbols: n-number of individuals; % - percentage; MJD- Mseleni Joint Disease

Percentage prevalence calculated within columns for gender. X² were used to assess the association between MJD, demographic and spatial variables.

Table D6. Frequency distribution of Mseleni Joint Disease relative to age categories for studies identified in the meta-analysis, and data from the medical record review conducted in this study.

| | Age (years) | MJD positive | | MJD negative | | Total |
|--|--------------------|--------------|----|--------------|-----|----------|
| | | <i>n</i> | % | <i>n</i> | % | <i>n</i> |
| Fellingham <i>et al.</i> , (1973) [‡] | 0-10 years | 18 | 2 | 737 | 98 | 755 |
| Lockitch (1974) [‡] | | 4 | 0 | 1359 | 100 | 1363 |
| Yach and Botha (1985) [‡] | | 0 | 0 | 634 | 100 | 634 |
| McLaren <i>et al.</i> , (1987) [†] | | 3 | 0 | 656 | 100 | 659 |
| Dinkele (2019) [†] | | 0 | 0 | 18 | 100 | 18 |
| Fellingham <i>et al.</i> , (1973) [‡] | 11-20 years | 72 | 18 | 331 | 82 | 403 |
| Lockitch (1974) [‡] | | 29 | 3 | 1083 | 97 | 1112 |
| Yach and Botha (1985) [‡] | | 5 | 1 | 687 | 99 | 692 |
| McLaren <i>et al.</i> , (1987) [†] | | 0 | 0 | 630 | 100 | 630 |
| Dinkele (2019) [†] | | 0 | 0 | 72 | 100 | 72 |
| Fellingham <i>et al.</i> , (1973) [‡] | 21-30 years | 75 | 42 | 102 | 58 | 177 |
| Lockitch (1974) [‡] | | 54 | 9 | 517 | 91 | 571 |
| Yach and Botha (1985) [‡] | | 12 | 2 | 506 | 98 | 518 |
| McLaren <i>et al.</i> , (1987) [†] | | 0 | 0 | 392 | 100 | 392 |
| Dinkele (2019) [†] | | 0 | 0 | 115 | 100 | 115 |
| Fellingham <i>et al.</i> , (1973) [‡] | 31-40 years | 76 | 43 | 100 | 57 | 176 |
| Lockitch (1974) [‡] | | 76 | 22 | 271 | 78 | 347 |
| Yach and Botha (1985) [‡] | | 11 | 4 | 238 | 96 | 249 |
| McLaren <i>et al.</i> , (1987) [†] | | 1 | 1 | 180 | 99 | 181 |
| Dinkele (2019) [†] | | 1 | 1 | 124 | 99 | 125 |
| Fellingham <i>et al.</i> , (1973) [‡] | 41-50 years | 82 | 52 | 74 | 48 | 156 |
| Lockitch (1974) [‡] | | 155 | 31 | 342 | 69 | 497 |
| Yach and Botha (1985) [‡] | | 23 | 11 | 191 | 89 | 214 |
| McLaren <i>et al.</i> , (1987) [†] | | 1 | 1 | 103 | 99 | 104 |
| Dinkele (2019) [†] | | 8 | 7 | 107 | 93 | 115 |
| Fellingham <i>et al.</i> , (1973) [‡] | 51-60 years | 95 | 67 | 47 | 33 | 142 |
| Lockitch (1974) [‡] | | 125 | 40 | 191 | 60 | 316 |
| Yach and Botha (1985) [‡] | | 38 | 22 | 138 | 78 | 176 |
| McLaren <i>et al.</i> , (1987) [†] | | 3 | 3 | 89 | 97 | 92 |
| Dinkele (2019) [†] | | 21 | 18 | 96 | 82 | 117 |
| Fellingham <i>et al.</i> , (1973) [‡] | 61-70 years | 106 | 72 | 42 | 28 | 148 |
| Lockitch (1974) [‡] | | 72 | 37 | 121 | 63 | 193 |
| Yach and Botha (1985) [‡] | | 28 | 16 | 142 | 84 | 170 |
| McLaren <i>et al.</i> , (1987) [†] | | 23 | 17 | 113 | 83 | 136 |
| Dinkele (2019) [†] | | 14 | 19 | 61 | 81 | 75 |
| Fellingham <i>et al.</i> , (1973) [‡] | 71-80 years | 43 | 74 | 15 | 26 | 58 |
| Lockitch (1974) [‡] | | 29 | 57 | 22 | 43 | 51 |
| Yach and Botha (1985) [‡] | | 34 | 37 | 58 | 63 | 92 |
| McLaren <i>et al.</i> , (1987) [†] | | - | - | - | - | - |
| Dinkele (2019) [†] | | 22 | 26 | 64 | 74 | 86 |

Abbreviations/symbols: *n*-number of individuals; % - percentage; MJD- Mseleni Joint Disease; [†] Hospital-based surveys; [‡] Population based-surveys.

Percentages calculated within rows.

Table D7. Joints affected by bilateral and unilateral pain at onset and during the sampling period as reported by surveyed patients with Mseleni Joint Disease.

| | | Onset n (%) | Present n (%) |
|------------------------------|------------|------------------------|--------------------------|
| Hip | Unilateral | 20 (54) | 11 (30) |
| | Bilateral | 5 (14) | 24 (65) |
| | None | 12 (32) | 2 (5) |
| Knee | Unilateral | 16 (43) | 11(30) |
| | Bilateral | 8 (22) | 20(54) |
| | None | 13 (35) | 6(16) |
| Ankle/feet | Unilateral | 3 (8) | 0 |
| | Bilateral | 2 (5) | 7 (19) |
| | None | 31 (84) | 30 (81) |
| Shoulder | Unilateral | 2 (5) | 4 (11) |
| | Bilateral | 0 | 2 (5) |
| | None | 35 (95) | 31 (84) |
| Elbows, wrists, hands | Unilateral | 2 (5) | 5 (14) |
| | Bilateral | 2 (5) | 6 (16) |
| | None | 33 (89) | 26 (70) |
| Lumbar spine | Present | 0 | 12 (32) |
| | None | 37 (100) | 25 (68) |

Abbreviations/symbols: n-number of individuals; % - percentage; MJD- Mseleni Joint Disease

Table D8. Excerpts of responses about the onset of Mseleni joint disease (MJD) from patients, doctors and nurses.

| |
|---|
| <p>TIME OF ONSET: YEAR</p> <p>Patients</p> <p><i>“It’s what I’ve been saying that it started around the year nineteen-ninety something. Nineteen ninety-four... “ “Ei! I have forgotten. It’s been long. Ninety... Maybe ninety-one!”</i></p> |
| <p>TIME OF ONSET: STAGE OF LIFE/MEMORY</p> <p>Patients</p> <p><i>“I don’t remember well, but... When I was still a young boy, my knees were painful, but that pain stopped without me getting treatment.”</i></p> <p><i>“A long time... years. Because when I had children, it had already started feeling sore. There was some discomfort before, but I would be able to walk even though the pain would be occasional.”</i></p> <p><i>“It has been a long time now. What I’m saying is... It was after I had them [children] when they were adults.”</i></p> <p><i>“I grew up with no issues and with this leg not affecting me. Until it became painful when I was older and had kids.”</i></p> <p><i>“I was older. I was living at eMseleni.”</i></p> <p><i>“I was involved in car accident in 1999...So as time went by, when I was back here in Mseleni... So that’s how the issue started because the leg that I injured is the one that I ended up having an operation on.”</i></p> |
| <p>TIME OF ONSET: ASSOCIATED WITH AGING[‡]</p> <p>Nurses</p> <p><i>“Yeah, from... Especially from forties and above. Yeah. But rarely, the thirties also.”</i></p> <p><i>“It affects the older people, forty years and above.”</i></p> <p><i>“From fifty upwards.”</i></p> <p><i>“What I’ve noticed here... Most of them they are fifty-five. Fifty... fifty-five.... In, in my community, seventy is expected to be older, but here in this community fifty-five, sixties they come for operations here.”</i></p> |
| <p>Doctors</p> <p><i>“Ah, I’ve seen most of the time is the elder patients, the elderly patients. So, your patient around the full tier ah, seventy-year-old.”</i></p> <p><i>“Certainly, they’re not complaining of the symptoms suggestive of MJD. But they are a younger population. I mean, there’s most of our women [in maternity ward] would be under forty so... and a lot of them would be under thirty... so you would find the younger population wouldn’t be complaining as much.”[†]</i></p> <p><i>“I do find that mostly the [early onset] joint pain is in obese patients. So, it’s difficult to distinguish between whether it’s an early type of MJD over whether it’s actually just extra weight on the joints.”[†]</i></p> |
| <p>TIME OF ONSET: CHANGE IN ONSET AGE[‡]</p> <p>Doctors</p> <p><i>“So, um, back in the day, I think it used to affect even youngsters. Um, late twenties, early thirties. But now I think we haven’t really had a lot of new diagnoses. So, I think the, the group that we still have are more the advanced ages and it’s mostly that generation that is progressively getting older. Um, and then I think, I think we have less young patients now with MJD.”</i></p> <p><i>“I was seeing people at that age group – twenty-five, twenty, twenty-five, thirty years old with, with Mseleni joint disease. Quite severe to the level of not being able to walk without sticks. And it has changed. Yes, I think, the population is aged. And we’re not seeing as many young people getting the disease.”</i></p> <p><i>“We’re just dealing with a cohort now that are aging. Some, some, some who had the disease 40 years ago. It’s the end, the tail end of the disease... Maybe, we’re not going to see twenty-year-olds with the disease, much in the future.”</i></p> |
| <p>MODE OF ONSET: PAIN AND IMMOBILITY</p> <p>Patients</p> <p><i>“There was some discomfort before, but I would be able to walk even though the pain would be occasional.”</i></p> <p><i>“The pain started when I was walking once. It was initially a sore knee, the knees were sore. After that, the joints [gestures to hips] became sore.”</i></p> <p><i>“When I was still a young boy, my knees were painful, but that pain stopped without me getting treatment.”</i></p> <p><i>“It was on my hip. It indeed started on the hip.”</i></p> |
| <p>Abbreviations/symbols: MJD- Mseleni Joint Disease; † Doctors reflect on their experience in the maternity ward when speaking about early onset of MJD.</p> <p>Excerpts from questions about the mode and time of onset of MJD (posed to patients) and age of onset (posed to doctors) (survey instruments in Appendix C.</p> |

Table D9. Excerpts of responses about the aetiology of Mseleni joint disease (MJD) given by patients, doctors and nurses at the Mseleni Hospital suggesting beliefs of environmental and lifestyle causes of MJD.

| |
|---|
| <p>SOIL/SAND/TERRAIN</p> <p>Patients</p> <p><i>“I don’t know? Some people say it’s the soil.”</i></p> <p><i>“Ei! I haven’t heard anything apart from the fact that it’s the soil where we live.”</i></p> <p><i>“It started like that until they later said it’s caused by the soil when they explain it. Because just like these ones [researchers]. I don’t even know how many times they would come looking for the cause of this thing.”</i></p> <p><i>“They say it’s caused by the sand but now there is sand everywhere... So that’s why I don’t believe in that theory. There’s a lot of sand in Manaba compared to here but they are still saying it’s the sand. I don’t believe in that.”</i></p> <p>Nurses</p> <p><i>“They think that maybe it's caused by too much sandy soil here”</i></p> <p><i>“So, at Mseleni, there is a lot of sand. So we think that maybe they really true. They are true. That is the cause of MJD... We think is that the cause, cause its more common at Mseleni.”</i></p> <p><i>“Ah, I'm not sure, but they said it's, they... it's the sand that they are walking on that causes the corrosion of bone and the... And this of the cartilage?”</i></p> <p><i>“I'm not sure, but what I heard before... it was the, the soil on the geographical area. That’s what we heard. Though, it was also not clear which way... It's what the community says and what the doctors think”</i></p> <p><i>“I don't know. They, they research, but they say it’s this soil, it's not having the iron.”</i></p> <p>Doctors</p> <p><i>“What about the food that is growing in the soil? Is the soil setting a problem with the food that we are eating? Because maybe there are toxic things that are already in the food.”</i></p> <p><i>“They talk about environmental and you're kind of thinking that it's quite an unusual, um, place to live in because it's all sand-based. And, I'm sure if you're living here and this is the normal terrain that you're coping with, it's probably related.”</i></p> |
| <p>ACTIVITY LEVELS</p> <p>Nurses</p> <p><i>“...And they were travelling from the young to older age. Without using a car. Walking 10 to 12 kilometres, carrying water on the head. Doing everything using their foot.”</i></p> <p><i>“It is the work we are doing, maybe. Also, it is long working hours. ... Hey, we are doing different work. We are working at the contracts; we are working at the hospital. We stand for a long time, maybe I might end up having MJD. Maybe, I'm not sure?”</i></p> <p><i>“I, I think it's the life [in Mseleni]. Not born with. “</i></p> |
| <p>DIET/WATER SOURCE</p> <p>Doctors</p> <p><i>“Alcohol, plays a role”</i></p> <p><i>“It might be that, um, that their nutritional deficiencies that they had then, which are not here now because we have a much different diet...”</i></p> <p><i>“...Less people growing things 'cause the land doesn't yield it well... So you can't really see a kind of trend there.”</i></p> <p><i>“I would think maybe it's related to what people eat, you know they plant, plough, eat. Or the type of water that people drink... The type of water that we drink, it could have those minerals...”</i></p> <p><i>“... because there is a river Sibhayi, is it coming from the river? We don't know. ”</i></p> <p><i>“You have already an idea that this place is it is predisposing to this condition... Because I was just thinking why just, it's often this side of KZN [KwaZulu-Natal]. What is in this area of KZN?”</i></p> <p>Abbreviations/symbols: MJD- Mseleni Joint Disease; KZN- KwaZulu-Natal Province Excerpts from questions about the aetiology of MJD, from survey instruments in Appendix C.</p> |

Table D10. Excerpts of responses about the aetiology of Mseleni joint disease (MJD) given by patients, doctors and nurses at the Mseleni Hospital reflecting beliefs of biological and physiological causes of MJD.

| |
|--|
| GENDER |
| Doctor <i>"But I think we still we still, still see a majority of women. But there's, there's two ... bit of problems with that because it's just an impression. And I mean basically the hospital always sees more women than men for almost everything. Could be partly expressed on that, but, but, in in surveys that have shown that you know there are, ah, more... higher percentage of women have their arthritis than men. There's a shortage of men. Adult men in the population compared to women anyway. It's probably. You know two to one, or more..."</i> |
| AGE |
| Nurses <i>"It's not a child disease, it's for the old people" "It affects the older people, forty years and above."</i> |
| Doctors <i>"Besides the natural causes, which we cannot run away from. Old age does... Ah, some men... Ok, let me say, old age plays a role." "I mean, some of the people who are my age now, already had the disease then. I was twenty-five. Some who are still developing it, but they're usually now in the thirties, forties and beyond. So maybe they were affected but not actually demonstrating disease at that stage, and its taken longer to develop"</i> |
| GENETICS |
| Doctors <i>"Yeah, so I was thinking also MJDs, why only this side? You can also think about the genetics, how people are getting married. Maybe this one can be married by the cousin and cousin. Genetics cannot lie. Also, the genetics are very important. The other abnormalities are coming through genetics. That is my opinion..." "But I think we still, we still see a majority of women... in surveys that have shown that you know there are, ah, more... higher percentage of women have their arthritis than men. There's a shortage of men. Adult men in the population compared to women anyway. It's probably. You know two to one, or more and so..." "They do talk about genetics."</i> |
| IMMUNOLOGICAL |
| Doctor <i>"What could be causing it? OK, um the cause. I can... most of the time is an inflammatory cause."</i> |
| JOINT ABNORMALITIES/ GAIT |
| Nurse <i>"I don't know, but, I think, I think it's the cartilage. You see that the cartilage in the joint, in the hip joint. Because it is not available, these bones are crushing each other, they make it painful."</i> |
| Doctors <i>"I think I will take it back to the way I thought before I became a doctor, right? The reason why I thought this is a Mseleni problem. It is 'cause of the way how most gogos [elderly women] and mkulus [elderly men] ... So those are like grannies... How most of them used to walk or how they walk when they have this joint problem. It is, it's a typical walk..."</i> |
| <i>Zulu terminology: Gogo- Zulu term for an elderly woman; Mkulu- Zulu term for an elderly man Excerpts from questions about the aetiology of MJD, from survey instruments in Appendix C.</i> |

Table D11. Excerpts of responses about the aetiology of Mseleni joint disease (MJD) given by patients, doctors and nurses at suggesting beliefs of spiritual and social causes (MJD).

| |
|---|
| WITCHCRAFT/ SOCIAL FACTORS |
| Patient <i>“Well, this started like this. When it enters someone, they would say that they have Umeqo†. You remember right? Yes, something painful will entered my leg.”</i> |
| Doctors <i>“Witches, this kind of things is happening. Is that person who did this to me, that person did this to me. So they want to resolve the problem first in the community.”</i> <i>“In this community, there is a belief that there is a condition called Umeqo. So Umeqo is, um, when a witch basically, casts a spell on a path that you're gonna' walk on and as soon as you step over that spell then you may have issues with your legs and mobilization. And. So it's likely that as the MJD develops, that can be viewed as some form of um, witchcraft or sorts.”</i> |
| ACTIONS OF ANCESTORS |
| Nurse <i>“Okay, yeah, sometimes they think they are being punished by the ancestors and so they will do maybe, ceremonies and other rituals for the ancestors.”</i> |
| <i>Abbreviations/symbols: † Umeqo is the cultural belief that one can be bewitched from walking over an object that has been cursed. Excerpts from questions about the aetiology of MJD (survey instruments in Appendix C).</i> |

Table D12. Excerpts of responses given by patients, doctors and nurses linked to the pathophysiology or mechanism of Mseleni joint disease (MJD).

| |
|---|
| ACCUMULATION OF BAD BLOOD |
| Nurse <i>“Yeah, and when that, is that swelling. Um, they think there is the bad blood that has accumulated there. So when they cut it a little bit to make those caba marks, that blood that bad blood will come out.”</i> |
| IMFLAMMATION AND JOINT CORROSION |
| Nurse <i>“The sand that they are walking on that causes the corrosion of bone and the cartilage”</i> |
| Doctor <i>“Although it's not an inflammatory arthritis, you know once you've got wear-and-tear it creates inflammation”</i> |
| <i>Excerpts from questions about the disease process and cause of MJD (survey instruments in Appendix C).</i> |

Table D13. Excerpts of responses about the symptoms of Mseleni joint disease (MJD) from patients, doctors and nurses.

| |
|---|
| CHRONIC PAIN |
| Patients <i>“I can go to the garden. But I go with pain, but I still persist, stubbornly. So that I can farm/garden. Maize, I eat samp, nuts... but now I cannot do that because of the pain, as soon as I stand, I have to sit this way. Even my arms become weak like these legs... When I'm seated as I am, it isn't painful, when I get up that's why I can feel them. That's when I realize that this area is sore before of MJD.”</i> <i>“Like for instance this one has become weak but it's pain, it's not like this one[hip]. This one is being hurt by the metal. I can't bare it, even when I sleep.”</i> <i>“Mmm. I will say they are helping because when the pain is high, when I take them it becomes better. But only for that time.”</i> <i>“It [MJD] has affected me because when you're felling a constant pain even if you take medication... So, we started with the traditional route, do you see these cuts, they did this saying that they were healing us saying that it will end but it never stopped. I only knew pain that was different, and which was slightly better after surgery. Because it's like the blood they removed from this region they operated... I don't know. But, I felt a difference because when I came back after the first surgery”</i> |
| Nurse <i>“They're complaining of pains, mostly, pains, yeah, especially when they are walking.”</i> <i>“Some of them will have, some sores, because this prosthesis is protruding out and is grating the skin.”</i> |
| Doctor <i>“But I... most of the cases you see, they will tell you that, they, they have history of joint pain for so long.”</i> |

IMMOBILITY AND GAIT

Patient

"The limping began at that time and then eventually the pain went onto the other leg. Both were painful."

Nurse

"I just both, it's, it's pain on when they're moving like this [gestures a shuffling movement] when they walking on the joints, the stiffness of joints."

Doctors

"Well, yeah, I, I think one of the one of the big things that we used to see was, was severe joint constrictions. Where you had flexion deformities or windswept deformities without any having had any physiotherapy. When your joint is painful, you don't move it. When you don't move it, you keep it in a flexed position. Usually if it's a hip or knee, you will tend to flex it. If, if you flex it and keep it still, you'll get shortening of the, of the, of the muscles, and so you'll get contractures which will make it more and more difficult to move the joint. And the more difficult get smooth the joint the more deformity happens."

"So, from my experience, most MJD patients they come with, they come with this posture that's different and the walk. You see them from, from far. When they're walking you can, you could spot, this person is suffering from an MJD problem."

"I am sure Dr X told you about the tell-tale signs. Um, they'll usually walk with a limp, but it's not a usual limp that they walk in, it's sort of a swaying gait from side-to-side. And then as time goes on, they um, develop sort of a... an adduction at their hips, so they basically can't open their legs and when they're walking, it's sort of like a sliding motion between the two legs and the because of that, their knees then tend to abduct and accommodate that so... I think, I think, I think it is an accommodation for the pain. Yeah, if they feel pain then they're 'gonna... their gait, they're 'gonna change the way they walk to accommodate pain."

"So, I would see from that walk that, OK, this patient may have this problem [MJD] and then we take history."

Abbreviations/symbols: MJD- Mseleni joint disease; Dr X - A pseudonym used to anonymise a specific doctor referred to by name.

Excerpts from questions about the symptoms occurring during the course of MJD (survey instruments in Appendix C).

Table D14. Excerpts of responses about the anatomical localisation of joint pain in Mseleni joint disease (MJD) from patients, doctors and nurses.

AFFECTED JOINTS

Patients

"But now the pain is on this one [left hip], that hasn't had the metal removed the one that I started with however I just have to struggle with it... but it's sore."

"The pain started when I was walking once. It was initially a sore knee, the knees were sore. After that, the joints [hips] became sore. I would feel pain when I was walking. The limping began at that time and then eventually the pain went onto the other leg. Both were painful."

"The pain ... is on my hip, the one on the left. But also, then again when it's going to rain or the weather conditions have changed or will change"

"Yes. But also this one [left] has started deteriorating. Both my feet (or an area on the lower limb) and my knees. My hands also, they would get cramps?"

Nurses

"They were complaining about painful hips"

"They usually report the pain in the joint. In the joint. Yeah, on the hip joint, yeah. Maybe it's one, others are both."

"It's mostly the hips, mostly the hips. Mostly hips... the knees are not that frequent."

"No, I haven't heard that one [upper limb joints], not unless it's a typical type of arthritis."

"It's the hip, especially the hip. Yeah, most of them."

"On the joint [hip]. Sometimes, they're complaining of the one. But some, they are saying both of the joints."

Doctors

"Also, the, the more classical MJD tend to have fairly... It's not a one joint, it's not one hip, it's both hips and they're fairly similarly deformed and destroyed. And by the time you got, a, a, severe arthritis in one, you got significant arthritis in the other. Generally speaking... Whereas with OA you may have just one joint that's bad and the other ones perfectly normal."

"But yeah, and most of them. They present with hip problems."

Abbreviations/symbols: MJD- Mseleni joint disease. Excerpts from questions about the localisation of joint pain in patients with MJD (survey instruments in Appendix C).

Table D15. Excerpts of responses about the psychosocial effects of Mseleni joint disease (MJD) given by patients, doctors and nurses.

| |
|--|
| <p>SEXUAL INTIMACY</p> <p><u>Nurses</u></p> <p><i>“Cause the hip used to be stiff. The, the hip or the, the knees. So, then they would be unable to open [during sex].”</i></p> |
| <p>STIGMATISATION IN COMMUNITY</p> <p><u>Doctors</u></p> <p><i>“So if it is a younger population, you may find that they're not, uh, sympathetic towards those women that or sorry those patients because we're not talking about women, but those people who, who are having the condition. Whereas you kind of look to older people with the joint disease and you're on your kind of saying, well the gogos' [grandmothers/older ladies] are sitting at home and they're being cared for, but they're not expected to do a huge amount. But if you are like the daughter-in-law, you're expected to carry your weight, you're expected to do the work. Um, and she may not. They may not get as much support from their in laws. That's a very rural African kind of thought on, on how the family dynamics work.”</i></p> <p><i>“I've stayed with the community, with someone who had it [MJD]. There was no stigma. I, no, I don't remember anything of that sort.”</i></p> <p><i>“I think the immobility part becomes sort of the point of stigmatization. For instance, I remember someone in the community had two wives, one of the wives didn't have MJD and then the other had MJD. So it was almost like this one [with MJD] was the lazy one, just because she couldn't mobilize. So, I'm sure you've heard of the makoti [bride or newlywed woman] phenomenon within this community. So, if you are a makoti, you are supposed to like work from dusk to dawn, and you're supposed to never get tired. You're supposed to be looking after the kids and looking after the fields, looking after the yard, looking at your husband and everything else in between. So, within this household everyone knew that the, the one that was normal was doing all the chores, but this one [with MJD] was a lazy one 'cause she was always sitting on her bum. So then you know those discrepancies come in where you, you are not doing what you want to do, or you are not doing what would normally be viewed as normal because of your limitations. But other people out there may not necessarily understand the pain that you are in, because you probably don't have a wound or you didn't have an accident. So, they don't accept the fact that you are disabled by the condition that's going on.”</i></p> <p><i>“‘Cause it will almost be like, oh it's a shame, she's got a sister-wife who can't do that. And you know, um, then eventually they thought the, the disabled one was now bewitching the other one 'cause she was jealous.”</i></p> |
| <p>LOSS OF INDEPENDENCE</p> <p><u>Patients</u></p> <p><i>“I don't except this for my own child. She's someone's child, what I mean to say is she has a child with my child [daughter-in-law]. She helps me, but before she was here I used to struggle for myself.”</i></p> <p><i>“My son's wife goes [to collect water]. How could I do it since I walk like this?”</i></p> <p><i>“It has affected me greatly because I used to farm a lot. When I was affected, I used to think how am I going to live now? Because farming sustained my livelihood.”</i></p> |
| <p><u>Nurses</u></p> <p><i>“You, you know, sometimes the older people, they end up staying alone with their kids, having their family somewhere else.”</i></p> <p><i>“Then I must look for someone. I get somebody to look after her. But before that, they are all by themselves at home, most of them.”</i></p> |
| <p><i>Abbreviations/symbols/terminology: MJD- Mseleni joint disease; Makoti- Zulu term for a newlywed woman or a bride; Gogo- Zulu term for an elderly woman.</i></p> <p><i>Excerpts from questions about the course of MJD and its impact in the patients and community (survey instruments in Appendix C).</i></p> |

Table D16. Excerpts of responses about the socio-economic impact of Mseleni joint disease (MJD) given by patients, doctors and nurses.

| |
|--|
| UNEMPLOYMENT |
| <p>Patients <i>“Currently they [daughter] are no longer working in Mseleni [hospital] because when they [daughter] stand on their feet it becomes too painful. So, they stopped.”</i></p> |
| <p>Nurses <i>“I’ve decided to go to Mandeni to collect her daughter so that she can come and stay with her mom. And she [the daughter] has decided not to go back to work, she’s saying at home with her mom... ‘cause I’m working and it’s not my mother-in-law. It’s my mother-in-law’s sister. You see?”</i> <i>“Yeah it has a great impact, especially on breadwinners. Because, due to the speed of recovery or the patient he doesn’t recover... There’s not that speed recovery [to allow] going back to work. Others may be being terminated or retrenched.”</i> <i>“It, it affect them and their families because they all end up not working.”</i> <i>“Yeah, yeah, walking becomes a problem. The main problem, which leads them to become unemployed. It’s high unemployment at an early stage for your retirement age, that will also bring poverty. Then poverty to the family result to the property of the community as well.”</i></p> |
| <p>Doctors <i>“Depending on the patient himself first, because if the person is the breadwinner, you will understand that everything will fall apart because it’s not going to be available as usual for his family or her family.”</i></p> |
| EDUCATION |
| <p>Nurse <i>“Because here as we see, most of patients come here, they come like grandmother with a grandson or granddaughter. It’s affecting a lot, and then she has to be here every time. She’s not going to school.”</i></p> |
| <p><i>Excerpts from questions about the impact of MJD on patients and the community (survey instruments in Appendix C).</i></p> |

Table D17. Excerpts of responses about the diagnosis of Mseleni joint disease (MJD) given by doctors Mseleni Hospital.

DIAGNOSTIC PROCEDURES

Doctors

"No, I don't think you can [distinguish OA from MJD]. There isn't a diagnostic test and I, I think it's one generally uses the idea that you know if you're seventy-five or eighty and you just recently got, you developed arthritis, in these last ten years then it probably could just be ordinary OA like everybody else in the world suffers. But if you developed it when you were thirty-five or forty, then it would be less likely."

"It's a it's sort of a bit of a, phenomenology with a rule out of other known pathologies. So, if you can see they've got TB, if you can see they've got gout. If you can see they got rheumatoid, or they've got a congenital abnormality of the bones then you would rule them out of being MJD. So one of the ways you know a joint is painful, as you can see, all these scarification marks around it."

"No, when you see. When a patient comes OPD, of course, you need to take history, examine, make a provisional diagnosis, at least one, or two, or three. If needs be, you investigate, then you treat. Of course, we X-ray the patient, of course you might collect blood if you suspect some other arthritic-related pathologies. Just like rheumatoid arthritis, gout arthritis that is the first thing you do. To exclude, if not those ones."

"But a patient to me who comes with either, elbow, shoulder, knee, ankle joint-related problems. I approach them the same way. Unless I can maybe getting some advice to say, this one we can classify as MJD. Any arthritic patients for me is the same. I never see I cannot differentiate like I said."

"As far as I'm aware, there's not, um its just doing the normal history, examination, X-rays."

"It's the history, and then your clinical examination and then would use then X-rays to get to, to the final diagnosis and say this is the MJD. They present with hip problems. So I would see from the walk that, it's a typical walk if you look at them you say, this is Mseleni [Joint Disease]. And most of these gogos you would see them here in this area and then they come for an X-ray, boom, you see a joint problem. And it's a typical walk. I've never seen it anywhere else. I've never seen it anywhere else, except here."

"So generally it's just a basic history, examination. But then coming to the hospital then you look for particular X-ray findings and some of those are basically flattening of the acetabulum. Then the head also flattens, the head of the femur flattens following the flattening of the acet... acetabulum, with decreased joint space and sclerosis, um periarticular. To a point where some patients actually have no during space at all, and sometimes it's unilateral. Sometimes it's bilateral. Sometimes it may be bilateral, but one hip is much more effected than the other, so yeah. Biochemically, there, there isn't any particular findings that I know of..."

"But in clinics they mostly refer patients, that knows they have OA. And then when you evaluate them, when you do X-rays then you find out that- no, this is a special problem. Actually, what we do is... When a patient comes and then you examine first and then you see how far they can be able to mobilize to join. And then there's any limitation of range of movements and then so, you do the full assessment on passive and active assessment of joint."

"So basically, you what I do like myself, I see if the patient can be able to stand, I assess the gait, and if they can be able to walk properly. Then you do bloods, check if they're not developing any metastasis somewhere here, that came from somewhere else."

"If someone coming for joint pain, then you can relay the patient straight to Dr X. So, when Dr X is there, he can see the patient. But if we consult the patient, we have a patient with the joint pain and then you do an X-Ray. After assessing the patient clinically, do an X-ray. And then you can conclude that the patient can have the MJD and you, then you refer to Dr X and he will confirm."

"I'm not sure exactly how to actually diagnose MJD compared to other joint diseases. So I think we'll do like a basic arthritis work up, usually X-rays, rheumatoid factor, inflammatory markers and then, depending on what you find on that. If there's an obvious breakdown in the joint, then we will discuss with Doctor X or we'll discuss it with Orthopedics at Ngwelezana."

"I mean obviously try, try to exclude all the other like more common causes of like, hip pain. And if that, those are all excluded and then we would then consider the diagnosis of MJD."

Abbreviations/symbols/Zulu terminology: OA- OA, MJD- Mseleni joint disease; Gogo- Zulu term for an elderly woman; Mkulu- Zulu term for an elderly man.

Excepts provided were from questions posed to doctors about the diagnosis of MJD (survey instruments in Appendix C). Dr X - A pseudonym used to anonymise a specific doctor referred to by name

Table D18. Excerpts of responses about the treatment of Mseleni joint disease (MJD) given by patients, nurses and doctors Mseleni Hospital.

| PHAMARMACOLOGICAL TREATMENTS | |
|-------------------------------------|--|
| Patients | <p><i>“Here they just give us these ones. We call them amodolo, they’re greenish on one side and yellowish on the other. Those are the ones they give us.”</i></p> <p><i>“Yes, I take pills. They gave you the red ones and the white ones, Panado?”</i></p> <p><i>“Just medication for blood pressure and pain killers”</i></p> <p><i>“I don’t think there is anything else that could help me except for the pills I’m already using.”</i></p> <p><i>“I will say they [tablets/medication] are helping because when the pain is high, when I take them it becomes better. But only for that time.”</i></p> |
| Nurses | <p><i>“Their commonly get the strong analgesics.”</i></p> <p><i>“Eh, but they, others they can move. But painfully even using the stick. Others they manage the pain. By taking brufen® and... and eh, indocid®.”</i></p> |
| Doctor | <p><i>“Um, well it depends on the severities. I will talk on behalf of arthritis. It depends on the severity of the arthritis as it differs from person to person. There are those who have severe pain where of course you start using injectable, eh, anti-inflammatory drug. From there you can give also non-steroidal anti-inflammatory agent with paracetamol.”</i></p> <p><i>“The patients may go to any of those situations so they can go to a mobile clinic and get analgesics. They will see a nurse visiting for the day”.</i></p> <p><i>“Although it's not an inflammatory arthritis, you know once you've got wear-and-tear it creates inflammation. Particularly joints like the knee, which is a fairly unsupported joint. It gets it [steroidal injection]. It certainly does give a pain relief and improvement, patients certainly appreciate it.”</i></p> <p><i>“So what we recommend is taking the analgesia and moving through the pain, so we try to encourage range of motion.”</i></p> <p><i>“So it's mainly analgesia. Um, so, your paracetamol, non-steroidal, brufen®, and we have naproxen® here as well. And then of course with the ones that have hypertension, we try and not put them on nonsteroidal. So, um tramadol® and then some rubbing.”</i></p> <p><i>“I mean, I think definitely pain intervention because they are feeling like a chronic pain. They do take their, their tablets.”</i></p> <p><i>“Yeah, so it's normally analgesia. Give further treatment or manage the patients a bit better than at clinic.”</i></p> |
| THERAPEUTIC TREATMENTS† | |
| Patients | <p><i>“Yeah. I’ve gone there for physiotherapy. It did help me. I ended up stopping, I felt much better.”</i></p> <p><i>“The doctors gave me these booklets to see what exercises I can do. So I do what they said I should do. And then I just kick.”</i></p> <p><i>“I stopped going because it felt like they were just finishing me off when they were doing it.”</i></p> <p><i>“The hospital gave him the wheelchair and they would come and check on him from time to time.”</i></p> <p><i>“Because I started by using this stick then I started struggling then they gave me this [walking frame].”</i></p> |
| Nurses | <p><i>“Eh, but they, others they can move. But painfully even using the stick.”</i></p> |

Doctors

“So, but, range of movement, I think trying to maintain range of movement is one of the things we recommend and so that means you take the analgesic. But then you move as opposed to taking the analgesic and staying still. But obviously physiotherapy is, I think probably a key component for early arthritis. And that's what I would encourage for the use of analgesia and motion...”

“What does make a difference [post-operative recovery] is the speed of mobilisation. We have moved from, no weight bearing, not walking, staying in bed, getting out of bed to walking from the theatre table, almost, you know. So people on day one will actually get up and walk across the floor in the ward - with support and, and control but... Not just wrapping the knee up but actually immediately post up the physio, does a visit and flexes the knee. We aim for 90° of flexion in the, in the knee and hip we, we flex, but we don't over flex.”

“It probably depends on who sees them, but a lot of us will refer our patients through for therapy as well as normal pain relief.”

“And then a lot of reha... rehabilitation. So, physio [physiotherapy], mobilization. A lot of them walk with aids, so stick, crutches, walking frames. Um, yeah some of them actually end up being wheelchair bound, so yeah.”

SURGICAL TREATMENTS

Patients

“He sat in a wheelchair because he was disabled after the two surgeries. He could no longer walk with sticks, so he was wheelchair bound.”

“I've had surgery on both legs. Which means this one was operated and corrected it and then it wasn't well, so I went to Dr. X and he removed the metal. But now the pain is on this one [left hip], that hasn't had the metal removed. The one that I started with [right hip] I just have to struggle with it, but it's sore.

“They operated three times. First to insert the metal, to replace it, and then to remove it. And I went mad, I don't want to anymore! I have had too many operations.”

“I only knew pain that was different, and which was slightly better after surgery. But I felt a difference because when I came back after the first surgery, I found out where my hip bones lie, they really opened me up it's scary.”

“Many times [speaking to surgeries]. The number of stitches on my body, just here on my hips are ten. Five this side, five that side”

“The way the hip was under strain, I suspect that the bone that the metal part goes into [was] busted, the way things happened. Because when I was awake and Dr X was relocating it, it was never the same... it was never the same.”

Nurses

“Maybe it's due to operation of an old, old person we are making. They have other, other condition except the MJD. The other they have diabetes, others hypertension then we operate they are complicate.”

Doctors

“For long before they're immobile, I think you probably once you're at a stage where you got severe pain that goes throughout the day on the nights and you can't move without pain I would prescribe total joint replacement. My criteria will be significant pain that's damaging your lifestyle. That's causing you to have to use analgesics all the time and disturbing your sleep, making... limiting your activity.”

“You send them for X-rays. You look if there is any hope of that patient to regain again from fully function motion. So, the criteria, when you have all those information's then you decide. If they are around the fifties, sixties and seventies and then they still have chance to walk again.”

LIFESTYLE INTERVENTION

Patients

“These metals they put on my hip get sweaty because I spend too much time in the sun. They told me to try and decrease the amount of work I do but I don’t like sitting and doing nothing, my heart longed to do more work.”

Nurses

“Maybe, maybe we can prevent it by eating healthy foods.”

Doctor

“And obviously, weight loss is a big thing. The same as with any type of arthritis where we will advise weight loss, light exercise and then therapy too.”

Abbreviations/symbols/Zulu terminology: † Responses about to walking aids (wheelchairs and crutches) are included under Therapy, as they are provided by the therapy department at the Mseleni Hospital.

Amadolo- Zulu term for knees, colloquial term for tablets prescribed for joint pain.

Dr X - A pseudonym used to anonymise a specific doctor referred to by name

Excerpts from questions about the treatment of MJD (survey instruments in Appendix C).

Table D19. Excerpts of responses about the barriers to treatment of Mseleni joint disease (MJD) given by healthcare providers at the Mseleni Hospital.

| LIMITED TRAINING AND KNOWLEDGE |
|---|
| <p><u>Nurses</u> <i>“Not really, I started hearing about it when I, when I. Immediately after I started, a few years after I started being a nurse that there is something called Joint Mseleni Disease. Mseleni Joint Disease.”</i></p> |
| <p><u>Doctors</u> <i>“Initially, when I arrive, yeah even didn't know what's MJD. But I ended up asking what does it stands for, what does it mean? They, they told me about that arthritic-related pathology for people around seventy. But I knew about the Mseleni Joint Disease. But when they started abbreviating it... Until somebody when I ask was MJD they told me its Mseleni Joint Disease. You see?”</i> <i>“Maybe should I have been introduced? Yeah, maybe to say, hey, you know at Mseleni we've got JMD. Mseleni, whatever, joint disease...”</i> <i>“A lot of patients that clinic would just get labelled MJD because they got arthritis and any arthritis will be labelled MJD unless, unless specified otherwise. But if they're at the hospital they would get an X-ray.”</i> <i>“We don't, you know. I think the, the physiotherapy, occupational therapy around the disability of arthritis is very limited.”</i> <i>“I don't really think they [community] know, they know, some of them. They know that there's MJD. There's Mseleni joint disease, but the full understanding of it, I don't think that's there.”</i> <i>“So when you are in OPD, maybe for two hours and then you will refer the patient, you will never ever follow up with the patient. Unless you meet the patient in the ward. “</i> <i>“It was... I would say it was on, in the field training and that's referring to the first time I was here. And those that were severe having their hips [replaced]. Um, but now they also have the opportunity to do knees as well.”</i> <i>“There wasn't a specific orientation regarding it, but as, it's in the roster, and there are operations done, and you've seen patients in OPD, you kind of find out about it. So, it was more learn as you go type of thing.”</i> <i>“Most of them are either already on the programmes since they have been treated here for many years, or they are specifically seen by the orthopaedic team. Then I'm not sure exactly how to actually diagnose MJD compared to other joint diseases.”</i></p> |
| LONG REFERRAL PROCESS |
| <p><u>Nurses</u> <i>“Yes, yes. They have been eating analgesics for almost two years. Most of them...”</i></p> |
| <p><u>Doctors</u> <i>“Even before they are seen by the doctor and they'll have pain medication given by the nurses and then get referred through eventually. It might take a couple of weeks or it might take longer depending on their symptoms.”</i> <i>“They may get referred to the Doctor Residential clinic if the nurse feels that they need to see the doctor. I think a lot of patients just get analgesia and continue with it. But if they're having problems, severe problems walking, they may end up being referred.”</i> <i>“They'll pick them up, send them for an X Ray. Then that's when we pick them up, they come you, you go in the old notes you find out that they've been complaining about joint pain for so long, difficulty walking and all that. And then, ah, they also present late, you know. Late presentation, when you do X-ray, you'll see that the joints just destroyed and then there's nothing that you can do that to try to give them hope of walking again.”</i> <i>“So it's a far clinic. Then you have to come early in the morning, get a bus. And then you arrive here later, around maybe 6. To wait for the next day...”</i></p> |

"Maybe they [nurses] give them analgesics. And after that, the patient doesn't improve. And then they book for the MO [Medical officer] to see the patient on the appointment date and then the MO will see the patient."

"On the, on the patients book like no, this patient, I found that is saying maybe arthritis or something like MJD. I want us to refer for X-ray so I prefer that the patient is to be seen in OPD with his X-ray result. And then from the OPD, doctor will see the patient and then say, this one can be MJD and then refer to Dr X."

LIMITED RESOURCES

Nurse

"Usually, we have two in two weeks. Because... Dr X used to make arrangements in time for operations so they usually get admitted when they are due for operations, so we would not take more than two. That will be two in two weeks. The standard is two in two weeks because he didn't want to be to be overloaded in the operations and..."

"They only come to Mseleni Hospital. Yeah, yeah, even its Manguzi, they come here."

Doctors

"So here was a [MJD] clinic on Fridays. That Doctor X sees mostly patients that he did a replacement on and those patients had Mseleni joint disease. Most of them had the hip replacements, total or partial hip replacements. And knee replacements as well."

"But basically, patients we were going to Ladysmith, and in the beginning, in the early eighties, eighty-one, eighty-two, eighty-three, we had a worker employed who would assist by taking without you organize patients and take them over to Ladysmith, where they would spend a couple of weeks having an operation get rehabilitated and come back maybe. And so I suppose we were probably sending ten or twelve a year. Eventually, the Department of Health joined in the game and provided us with a budget for, for doing joint replacement. So we did, we did surgery here and they would come down and we spend a week and do four or five cases."

"We started with a big review of the cases that have been done with about 100 cases that had been done at Ladysmith over the years. But we have now got a group from Empangeni. Uh the Empangeni, Ngwelezane hospital now has quite a few more orthopaedic surgeons. In fact, five consultants there. Now there are a couple in private, and they're all interested in coming up. And so we're working."

"The need for more anaesthetic support, more blood."

"A number of patients were referred out for revision surgery because we thought maybe they would benefit from revision surgery. Results have been less than ideal, I think, and you know, somehow we came to the conclusion that maybe salvage operations would have been better for them."

"But I do think yeah, in terms of actually having a program in the Therapy Department, we, we have lost a lot of distance there and one of the reasons is. We have a high turnover of therapists on the physiotherapy side. We have one long term Occupational Therapist, but the Physiotherapy Department is basically in, out, in, out, in, out, in, out. So they can't really develop anything better."

"But yeah, I mean the team, the other team that, that, that we do cases with comes from outside the, the hospital. So we'll have two liaise and coordinate with them when they're available to come and assist us with the cases. But it will be like maybe two or three times in a month that we would do the joint replacements."

"As much as, I don't really think even our own doctors, you know some of them, they don't really understand the MJD program 'cause the other reason why I'm saying this is, is, this is a remote area, right? You, you get, you get doctors coming in and out. You know you get new doctors every once in a while, so I think it is difficult to say every time we have a new team of doctors, we gonna teach them about this every time cause."

"They do the orthopaedic slate here, when ortho... um an orthopaedic surgeon comes from good Ngwelezana and also assists with that."

SHORTCOMINGS OF AVAILABLE TREATMENTS

Doctors

"It can be more difficult because partly because the joints are generally more advanced destruction and the joint structure is often a lot smaller. So, the people tend to be fairly small and then they have quite deformed joints. So you get soft tissue problems. You have, prosthesis sizing problems and then you have a, you have a higher demand of a rural life on the joint afterwards. So, so yeah, the, the, the private guys from private coming they say look you know these joints are challenging joints compared to what we normally do. Because people usually get to surgery in the private, they get to surgery quite a bit earlier than a lot of the patients here."

“Ah, they've also tried medicines that are just sold by anybody, at pension pay-outs. There are lots of people touting yellow pills and red pills and blue pills. Pharmaceuticals that are being sold irregularly by people with no knowledge of their safety and risk.”

“A lot of people will use these pills. If you actually ask them, you will discover that they bought some red ones or some pink ones at the pharmacy, at at the market, at the pension pay-out.”

LANGUAGE BARRIERS

Doctors

“Language barrier as well, because they want, they want Zulu. With Zulu patients, if you speak Zulu directly, they are more open”

POVERTY

Nurse

“Yeah, especially those that do not get the grant, because they walk with difficulty, so they need to be hired a car to take them to the hospital.”

Doctors

“In those days more than we do now, I think there's more transport available, but they went to the hospital and they would be sent home on the bus. There is still very poor accommodation for people in this area. In general, standard of housing is not good. Facilities are not good at homes, electricity and water is still in short supply, particularly in areas that are affected with, with this disease [MJD], where there's a lot more poverty. So I think poverty is what part of the problem in terms of how people's lifestyle is affected.”

“Unless if they need to be admitted, that's when you can book a, a place for them. Then they come and the following day they can get an X-ray. So, I asked them to come tomorrow... At this time to come to get a bus and go to hospital. Sometimes they don't come.”

“Yeah, others... other patients staying far just the mobile clinic. Okay, so the way we, we are working here, the hospital and clinics. So, others patient are going to the clinic because they are near, they're near to the clinic. [In remote regions] the mobile clinic, mobile clinic is going there, and then if there is nurses who can give the patient medication. You see how you are hiding the condition. So, the time you'll be worse, is the time when you'll come to the hospital.”

“So it depends where the patient lives, distance from the hospital, some live far away. Then obviously they can't walk, they would rely on someone else taking them to the hospital. And if they don't have transport, they're not going to come here.”

Abbreviations: MJD-Mseleni Joint Disease; MO- Medical officer; OPD- Outpatients department, Dr X - A pseudonym used to anonymise a specific doctor referred to by name.

Excerpts from questions about the frequency of joint replacements in MJD patients and barriers to treatment of MJD (survey instruments in Appendix C).

Table D20. Excerpts of responses given by patients, doctors and nurses that mentioned the impact of COVID-19 on access to treatment and treatment-seeking behaviours.

| USE OF HEALTHCARE |
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| <p><u>Nurses</u></p> <p><i>“Yeah, most of the patients are, are complaining of this disease because since I came here, most of them are complaining even, even now. We are having that pandemic disease [COVID-19], they will come in to make bookings for, for the, for the operations. But I think Dr X can't do the operation, but patients are feeling more pain.”</i></p> <p><i>“I think it's [barriers to treatment] just the COVID. Its COVID-19. The only thing that causes that is COVID 19. The attendance was good. There were many, many patients that were coming for MJD. Yeah, but like due to COVID... Not so much.”</i></p> <p><i>“Due to COVID. It has been stopped, those procedures have been stopped. But, before COVID, I think four... four to five patients in a week, yes.”</i></p> |
| <p><u>Doctors</u></p> <p><i>“So now in the next three months we, we... Unfortunately, the theatre that was then closed down for renovations. Or supposed to be 3 months, it's taken a year and COVID as well, sort of stopped a lot of elective operations. So, we've had a year without surgery, which is unfortunate, but...”</i></p> <p><i>“Yeah, so we used to do them [arthroplasties] a lot. I mean, I think, before COVID time, we would do almost every week. We would have a case almost every week. And also, with our theatre that was, was being fixed we were unable to do like longer cases in between, because we were anticipating if we have an emergency. So what happens is we still monitor them. The ones that were planned for surgery were still given dates to come in for monitoring and see how bad... are they getting worse?”</i></p> <p><i>“We were unfortunate with this thing called COVID. So, the time COVID, I came here last year, the end of last year. So that time it was that... I think it was the festive season, I can see already they were just doing some elective cases.”</i></p> <p><i>“So, we've got a... orthopaedics slate that we used to do on Wednesdays. But during COVID, it's obviously not happening. Um and I suppose having a specific targeted clinic for them, which we've kind of lost throughout this year. Where one specific doctor is allocated to see them, knowing exactly what to do, what path to follow...”</i></p> <p><i>“Yeah, so during COVID, one of the theatres, so like our ortho [orthopaedics] theatre has been closed. We only do emergency C-sections [caesarean sections], so some of those patients were, um their surgeries were postponed 'til next year. So, they are only coming next year for their surgeries. And we're not seeing that much patients that were booked.”</i></p> <p><i>“Then they were not doing any elective cases. So, the only one patient that I knew is like a patient that we've done for the MJDs and then they come with complications and stuff.”</i></p> <p><i>“OK, but due to COVID and our theatre they haven't been doing these from when I've come, but yes.”</i></p> |
| MISINFORMATION AND FEAR |
| <p><u>Patient</u></p> <p><i>“I don't know I was supposed to get help for this leg but I couldn't go. Let me say I was cowardly. I was scared. Because of this disease that's out there [COVID-19]. Yes, I was supposed to go to Albert Luthuli Hospital in August. Dr X said I should come back after going there. Whether they operate me or not, he said I should come. But I couldn't go because of this disease... But I ended up going to apologize to Dr X for not going so that it doesn't seem like I was refusing help.”</i></p> <p><u>Doctors</u></p> <p><i>“I mean the [MJD] clinic is not open, so I think that's a... 'cause patients came and they said, ‘No, the other one said there's no clinic, MJD clinic. You must wait till COVID is finished, over. Then they would come.”</i></p> <p><i>“It's like half of them would come, only like three instead of the ten or fifteen that is booked.”</i></p> <p><i>“No. You know, so for MJD in particular, I think because we haven't been doing a lot of surgery, their clinics have also been limited, so we haven't actually seen a lot of MJD patients coming in. And I mean even with COVID itself, patients aren't coming in and like there are people that tell you a week or two later or I had flu-like symptoms.”</i></p> |
| <p>Abbreviations: COVID or COVID-19 – Coronavirus Disease of 2019. Dr X - A pseudonym used to anonymise a specific doctor referred to by name; Excerpts from questions about the frequency of joint replacements in MJD patients and barriers to treatment of MJD (survey instruments in Appendix B).</p> |

