UNIVERSITY OF CAPE TOWN
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Social determinants of comorbid depression among diabetes and HIV/AIDS patients at primary healthcare settings in Western Cape Province of South Africa

Dissertation submitted to the University of Cape Town
in partial fulfilment of the requirements for the
Master of Public Health degree (Health Economics)

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Plagiarism Declaration

DECLARATION

I, Sanet Tintinger, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

The co-occurrence of physical and mental health conditions poses a significant public health challenge globally especially in low- and middle-income countries (LMICs). In South Africa, diabetes, HIV, and depression frequently co-occur in an intricate manner, and the illness experience is largely shaped by the differences between individuals, communities, and provinces. Previous research highlights the influence of socioeconomic factors on the relationship between diabetes, HIV, and depression, although the focus has mainly been on the variability in health outcomes explained by individual-level factors. There is a need for evidence on the mental health outcome variations attributable to distinct contextual levels amongst patients living with HIV and/or diabetes. This dissertation assesses the socioeconomic determinants of depressive symptoms among patients living with HIV and/or diabetes accessing healthcare at the primary health care level in the Western Cape province. Furthermore, it examines the variation in depressive symptoms attributable to individual, household, and community levels among this sub-population.

Baseline data collected from participants in a cluster randomised controlled trial, the Project MIND conducted in the Western Cape, was used in this analysis. This study applied a three-level multi-level logistic regression analysis. Random intercepts were added at the household and community levels using grouping variables for household socioeconomic status and PHC catchment areas to account for the heterogeneity that exists across the levels of the data hierarchy. Four random intercept multi-level models were fitted sequentially. The estimated intraclass correlation coefficients (ICCs) were used to determine the proportion of the variance of the outcome attributable to the grouping- and individual-level variables for each model.

Overall, the findings indicate that the variance in depressive symptoms among patients with HIV and/or diabetes can be explained by differences at the household- and community-levels when controlling for individual-level factors. Higher odds of moderate to severe depressive symptoms were significantly associated with being female, secondary level education, and food insecurity. Lower odds of moderate to severe depressive symptoms were associated with harmful/hazardous alcohol use, increased social support, and increased self-efficacy.

This study highlights the importance of policies that simultaneously consider individual, household and community levels to address co-occurring mental and physical health conditions in the Western Cape. The findings support interventions at the primary healthcare level and in the community to bolster social support systems and self-efficacy, promote mental health from early educational years, prioritise gender-sensitive health programs, and address household food insecurity among patients living with HIV and/or diabetes with depressive symptoms.

Acknowledgements

I would like to thank the Health Economics Unit and the School of Public Health and Family Medicine at the University of Cape Town for the guidance which has enabled me to complete this course.

In particular, I would like to extend my gratitude to my supervisors, Dr Amarech Obse and Dr Lucy Cunnama. Their tireless support and encouragement enabled me to complete this dissertation.

I would not have been able to complete this course without the support and encouragement of my family, including Simon Dey, Susan and Sybrand Tintinger, and Susanet Smith.

Many thanks should also go to the researchers and research assistants whose contribution to Project MIND was fundamental to the success of this study.

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List of abbreviations

AIC – Akaike's information criterion

AUDIT – Alcohol Use Disorder Identification Test

ART - antiretroviral therapies

BIC – Bayesian information criterion

CASE – Center for Adherence Support Evaluation

CES-D – Center for Epidemiology Scale on Depression

CIs – confidence intervals

CSDH - Commission on Social Determinants of Health

DALYs - disability-adjusted life years

HICs – high income countries

ICCs – intraclass correlation coefficients

LMICs - low- and middle-income countries

MOS – Medical Outcomes Study

MLA - Multilevel analysis

NCDs - non-communicable diseases

OOP – out-of-pocket

PHC – primary healthcare

SSA - Sub-Saharan Africa

TB – tuberculosis

UNAIDS – United Nations Programme on HIV/AIDS

VIF – variance inflation factor

WHO - World Health Organisation

YLD – Years Lived with Disability

Part A: Study Protocol

1. Introduction

1.1. Background

Global life expectancy at birth demonstrates an unparalleled increase in the 21st century (United Nations Department of Economic and Social Affairs, 2020). Life expectancy has increased from 66.8 to 73.3 years since 2000, although in low- and middle-income countries (LMICs) this increase remains at least 10 years lower compared to high-income countries (HICs) (WHO, 2022b). Growing public health system challenges arise as ageing populations have a high burden of mortality and morbidity (WHO, 2022b). The global increase in life expectancy is coupled with a significant epidemiological transition, including a rise in epidemic infectious diseases, chronic noncommunicable diseases (NCDs), communicable diseases, and mental health conditions (WHO, 2022b). Indubitably, due to the increased survival rate of the population, the accumulated exposure to diseases and risk factors over a person's lifetime means that the share of the population living with multiple conditions will continue to increase in the future (WHO, 2022a).

The constant growth in chronic NCDs significantly enlarges the global health burden (United Nations Department of Economic and Social Affairs, 2020). The global share of deaths attributable to NCDs have increased from 61% to 74% since 2000, while the burden of these diseases is shown to have shifted from HICs to LMICs in recent years (WHO, 2022b). Diabetes mellitus is of increasing concern, given its growing prevalence – which is estimated to reach 642 million by 2040 – and its frequent co-existence with other chronic conditions (International Diabetes Foundation, 2015). indicate that there is a high prevalence of persons living with diabetes in LMICs, and particularly in sub-Saharan Africa (Thienemann et al., 2019).

Despite the major investments in the management of communicable diseases such as human immunodeficiency virus (HIV), tuberculosis (TB) and malaria, these diseases remain responsible for almost half of all deaths in LMICs (WHO, 2022b). A decrease in HIV incidence and HIV-related mortality, morbidity, and transmission risk is linked to the higher availability of anti-retroviral treatment (ART) globally (UNAIDS, 2019, Johnson et al., 2016). With effective global HIV initiatives, such as the UNAIDS 90-90-90 targets, approximately 86% of all patients using ARTs had viral loads of less than 1000 RNA copies/ml in 2018 (UNAIDS, 2019). South Africa aimed to achieve viral load suppression for 73% of the population living with HIV by 2020 (Johnson et al., 2016). Unfortunately, HIV prevalence in South Africa remains one of the highest in the world (20.6% of the general

population) with 7.7 million South Africans living with HIV in 2018, and only 62% of people living with HIV accessing ARTs (Simbayi et al., 2019, Conan et al., 2022).

Another essential contributor the global health and disability burden is mental health disorders (WHO, 2022b, Daré et al., 2019). Mental health disorders are the third most frequently diagnosed disease after cancer and cardiovascular diseases globally (WHO, 2022a). Mental illnesses account for 32.4% of Years Lived with Disability (YLDs), and for 13.0% of Disability-Adjusted Life Years (DALYs) globally (Vigo et al., 2016), and more than 25.0% of people living in developing countries suffer from one or more mental health disorders throughout their lifetime (Daré et al., 2019). High mental health disorder prevalence is especially worrying considering its high co-occurrence with one or more chronic physical diseases and its aggravating effects on the consequences of patients' physical health (Daré et al., 2019). Moreover, since 80% of people with severe mental health disorders experience difficulty accessing mental healthcare and are more likely to receive inferior care for their physical health problems, mental health disorders are estimated as the second highest cause of morbidity and mortality in LMICs (Daré et al., 2019).

1.2. Problem Statement and Justification

Morbidity and mortality from the co-occurrence of chronic physical and mental health conditions are challenges to health systems globally, and especially in South Africa, since healthcare remains fragmented and challenged by limited structural, technical, financial, and administrative capacity to effectively integrate chronic disease management (Mahomed et al., 2014). In South Africa, multimorbidity estimates demonstrate low to moderate levels (3%–23%) of multimorbidity in younger age groups and moderate to high levels (30%–87%) of multimorbidity in older groups (Roomaney et al., 2021). Chang et al. (2019) estimate that 69.4% of South Africans are living with two or more conditions, with the most common multimorbid profiles including combinations of cardiometabolic conditions (especially diabetes and hypertension), HIV and anaemia, and combinations of mental health disorders.

The effective prevention and treatment of mental health disorders remain challenging in South Africa. In a study conducted in 2019, 38.5% of respondents in South Africa reported at least one lifetime common mental disorders (anxiety, mood and substance use disorders), the most common being major depressive disorder (24.7%) and the median proportional annual persistence of mental health disorders was 80.0% (Bantjes et al., 2019). The overall probable depression prevalence in South Africa is between 14% and 38% with significant variations between provinces (Craig et al., 2022). However,

the treatment gap for mental health disorders remains large as only one in four people living with a common mental disorder receive treatment (Lund et al., 2010). Lund et al. (2010) demonstrate a significant inequality between South African provinces in the resources available for mental health care, which underscores the variation in health outcomes in different parts of the country. This variation necessitates context- and province-specific policy development for mental healthcare (Craig et al., 2022; Lund et al., 2010).

Mental health management is especially complex when considering the high co-occurrence of mental health and chronic physical conditions. A meta-analysis of studies that focused on people living with HIV in Sub-Saharan Africa (SSA) demonstrates a prevalence of depression ranging between 9% and 32% in this population group depending on the use of ARTs (Bernard et al., 2017). Studies reveal that persons living with HIV and depressive symptoms are more likely to have poor health status overall, including lower weight gain, higher risks of suicide, faster progression to AIDS and increased mortality (Abas et al., 2014). Depression among persons living with HIV is also associated with a lower likelihood of depression medication and ART adherence (Memiah et al., 2014), lower economic productivity, worsened social isolation, and increased difficulties in social problem-solving compared to patients living with HIV without depression (Akena et al., 2010). Despite major improvements in HIV chronic care and prevention, HIV remains an essential consideration for research in South Africa, particularly since the life expectancy of people living with HIV is increasing and this population group is more likely to face multimorbidity as they age (UNAIDS., 2019).

Further complexity is added to the management of comorbid HIV and depression due to the high co-occurrence of both these conditions with cardiometabolic conditions, especially diabetes. Conservative estimates in South Africa show that 6.5% of adults have diabetes and that a whole of society approach is required to effectively respond to this ever-growing burden on the health system (Department of Health South Africa, 2021). People living with HIV are increasingly confronted with comorbid diabetes although healthcare for co-occurring HIV and diabetes remains highly fragmented and policies fail to address the undeniable role that social and economic factors play in perpetuating the co-occurrence of these health conditions (Bosire, 2021). People living with diabetes are also increasingly confronted with comorbid depression. Depressive symptom prevalence among diabetic patients has been estimated as high as 46.6% in South Africa (Jansen van Vuuren and Pillay, 2019). However, in the updated manual of the management of diabetes in South Africa (Department of Health South Africa, 2021), there are no indications of the importance of screening for co-morbid

depression among diabetic patients, creating a risk that this important comorbidity remains unidentified and untreated at the primary healthcare level (Leone et al., 2012).

Effective policy responses are required for improved health outcomes for patients living with co-occurring physical and mental health conditions (Mahomed et al., 2014). Mental health conditions cannot be understood or treated effectively in South Africa without consideration of its co-occurrence with HIV and diabetes, nor can policies effectively address this co-occurrence of diseases without consideration of the contextual factors that cause, worsen, and sustain the poor health outcomes for this population group (Lund et al., 2010). Since the components of socioeconomic status which contribute to the relationship and outcomes of co-occurring diseases differ between countries and contexts (Leone et al., 2012), research that considers the contextual factors and identify at-risk persons and vulnerable groups is essential for effective policy responses (Bernard et al., 2017; Abas et al., 2014). There is a need to unpack the multifaceted contextual influences on co-occurring diseases and the impact of individual, household, and community level determinants of health outcomes for effective policy interventions pertaining to co-occurring physical and psychological health conditions in South Africa (Leone et al., 2012).

Thus, studying the covariates of mental health disorders is relevant in South Africa to inform policies that address not only the treatment of co-occurring diseases themselves, but also the varied contextual factors in which they unfold. The current study aims to add to the available evidence by identifying the socioeconomic determinants of depressive symptoms among patients living with chronic health conditions, including HIV and/or diabetes. The current study also aims to understand the variation of depressive symptoms explained by differences between the different levels of the context (such as households' socioeconomic status and community factors). The results of this study will add to the available literature on co-occurring depression amongst people living with HIV and/or diabetes to support policy development in the Western Cape province of South Africa.

2. Brief Literature Review

2.1. Co-occurring diseases: An increasing global prevalence

The prevalence of co-occurrence of diseases has been estimated in various HICs. A systematic review and meta-analysis of prevalence studies to determine multimorbidity among adults in community settings, the overall global prevalence of multimorbidity was estimated to be 37.2%, with more than half of the adult population (over 60 years) worldwide lived with multimorbid conditions (Chowdhury et al., 2023). The study found that prevalence estimates vary according to regions, with 45.7% of people living in South America, 43.1% of North America, 39.2% of Europe, and 35% of Asia live co-occurring conditions (Chowdhury et al., 2023).

The co-occurrence of chronic mental and physical health conditions is gaining increased attention from researchers globally. Barnett et al. (2012) show that as the presence of physical morbidities increases, the presence of mental health disorders also increases, especially in more deprived compared to affluent groups. In a study conducted over 17 countries, various associations between mental health disorders (particularly mood, anxiety, substance use, and impulse control disorders) and the diagnosis of chronic physical conditions were found to be statistically significant (Scott et al., 2016). Alcohol use and depressive disorders often co-occur with chronic physical conditions, which is associated with a higher risk of treatment non-adherence, lower quality of life, and poor health outcomes (Daré et al., 2019).

Research of disease co-occurrence in LMICs remains limited. Afshar et al. (2015) estimate the mean prevalence of multimorbidity in LMICs as 7.8%, while Arokiasamy et al. (2015) estimate the prevalence in six LMICs as 21.9%. Estimates show that multimorbidity affects 53.8% of the population of Bangladesh (Khanam et al., 2011), 65.6% of the older population of China (Zhang et al., 2022), and six out of ten adults in rural India (Gummidi et al., 2023). While LMICs face a rapid increase in the prevalence of obesity and NCDs, infectious and communicable diseases continue to represent a double burden on population health and health systems (Basto-Abreu et al., 2022). The burden of NCDs is increasing at a higher pace and in younger age groups in LMICs compared to HICs, with increased health-related complications in the economically active population group (Oni and Unwin, 2015). Beyond the economic impact, the higher co-occurrence of diseases in younger age groups heavily impact individual mortality risk, as well as quality of life, productivity, and life expectancy (Basto-Abreu et al., 2022; Wade et al., 2021, Oni and Unwin; 2015).

2.2. The co-occurrence of chronic physical and mental health disorders

The co-occurrence of health conditions has negative effects both on the individual and the health system (Alaba and Chola, 2013). Studies demonstrate associations between the co-occurrence of diseases and lower quality of life (Arokiasamy et al., 2015), as well as with higher rates of mortality (Gijsen et al., 2001), increased consultation rates and less continuity of care (Salisbury et al., 2011), higher frequencies of healthcare utilisation and higher healthcare expenditures (Bähler et al., 2015; Glynn et al., 2011), and increased hospitalisation rates (Bähler et al., 2015), compared to persons diagnosed with a single health condition. In LMICs and HICs alike, the co-occurrence of diseases has a significant impact on adult physical and mental health outcomes (Arokiasamy et al., 2015). Depressive symptoms are associated with suboptimal adherence to chronic disease treatment and difficulties coping with the diagnosis of a chronic health disorder (Sorsdahl et al., 2018; Myers et al., 2018). These effects are amplified in LMICs where there is a high prevalence of health risk factors including personal factors, behavioural choices, and socio-economic conditions; a higher co-occurrence between different chronic NCDs, including diabetes and hypertension; and a higher prevalence of communicable diseases, including HIV (Thienemann et al., 2019). These factors increase the risk of persons being affected by multiple chronic conditions and worsen their subsequent health outcomes (Thienemann et al., 2019). The complexity and high burden of co-occurring diseases require integrated management strategies for effective health system responses (Ameh, 2020; Mendenhall et al., 2017; Mahomed et al., 2014).

2.2.1. The integrated management of co-occurring diseases

Integrated healthcare management is an essential part of effective and sustainable health systems responses to this growing burden of co-occurring diseases. The World Health Organisation's global strategy on integrated people-centered health services (IPCHS) urgently calls for a paradigm shift to a non-fragmented and comprehensive approach to health system financing, management, and service delivery, to move away from hospital-based and disease-based curative care models (WHO, 2015). The IPCHS stresses that chronic multi-morbidity should not merely be treated reactively, but investments should be made to understand and address the socioeconomic determinants thereof for sustainable health system responses (WHO, 2015). Effective integrated care requires an appreciation of how social problems cluster with and affect medical problems, as well as an understanding that co-occurring diseases may be caused by different determinants and can present differently than singular disorders (Mendenhall et al., 2017). This is relevant in LMICs where health disparities are of concern and socioeconomic determinants of health are perpetuated through inequitable health systems.

Integrated chronic disease management is a feasible healthcare delivery model in LMICs where health systems are faced with high burdens of disease and limited resources, as it allows addressing multiple healthcare needs at one point of healthcare delivery, as well as enables sharing of capital resources, strengthening delivery and distribution by building on service commonalities, and aligning funding mechanisms (Atun et al., 2010). Integrated approaches to address multimorbidity improve access to care, coverage, responsiveness to patients' needs, health outcomes, and reduce inequalities (Watt et al., 2017).

In South Africa, the integrated chronic disease management model (ICDM model) was implemented by the Department of Health to leverage the successes of HIV treatment programmes towards improved service delivery and efficiency at the primary healthcare level (Department of Health, 2012). The ICDM model incorporates the management of communicable and non-communicable diseases and has delivered improved results in chronic disease record keeping, clinical guidelines compliance and improved health outcomes (Mahomed et al., 2015; Ameh et al., 2017). However, the fidelity of the implementation of integrated disease interventions is greatly influenced by contextual factors and a standardised approach will therefore not necessarily yield positive results (Ameh, 2020; Lebina et al., 2020). There are also persistent inequalities in the quality of and access to care between and within provinces, as well as between urban and rural areas, which are not appropriately addressed in purely curative healthcare responses to co-occurring diseases (Mahomed et al., 2014). Without addressing the socioeconomic factors that shape the co-occurrence of diseases, integrated chronic disease management largely remains a reactive response to the growing health systems burden imposed by co-occurring health conditions.

Therefore, it is recommended that service coordination and integrated management of diseases in South Africa should include addressing the interaction between the socioeconomic determinants of health and chronic diseases (Mendenhall et al., 2017). Research in South Africa shows that integrated chronic disease management can be an effective health system response to co-occurring diseases (Ameh, 2020; Mendenhall et al., 2017; Mahomed et al., 2014). However, there is a need for ongoing research into the determinants of co-occurring physical and mental health conditions to address the varied contextual realities in which it unfolds and to allow for context-specific approaches to integrated disease care (Ameh, 2020; Lebina et al., 2020; Mendenhall et al., 2017).

2.3. Determinants of co-occurring diseases

A large body of research has been conducted on the various determinants of co-occurring diseases. Common predictors of multimorbidity in developed countries include socioeconomic status and

educational level, personal traits such as age and body mass index, behavioural factors such as medication adherence and physical activity levels, and persons' interpersonal network and marital status (Chen et al., 2022). In LMICs, multimorbidity has been associated with the higher body mass index and lower fresh fruit consumption (Zhang et al., 2022), lower educational levels (Arokiasamy et al., 2015, Khanam et al., 2011, Afshar et al., 2015), with persons who are single and those living in the non-poorest quintile (Arokiasamy et al., 2015, Khanam et al., 2011). Alaba and Chola (2013) found that South African adults with multimorbidity were mostly female (74%), had lower levels of education, lived in urban areas, were recipients of social assistance, and were unemployed. The authors found a strong positive association between multimorbidity and household income, healthcare utilisation, depression and obesity (Alaba and Chola, 2013). In a study conducted with chronic disease patients in South Africa, a higher risk of having a common mental health disorder was associated with being a female, unemployed, younger, living with HIV, and being food deprived (Petersen et al., 2019). Research in various contexts demonstrates significant differences in the covariates and determinants of co-occurring diseases, as briefly summarised below.

2.3.1. Individual-level factors

Evidence in HICs and LMICs highlights the association between older age groups and an increased prevalence of co-occurring diseases (Barnett et al., 2012, Arokiasamy et al., 2015, Bähler et al., 2015). However, a considerable increase in the prevalence of multimorbidity in the population below 65 years of age has also been found (Barnett et al., 2012, Afshar et al., 2015, Alaba and Chola, 2013, Thienemann et al., 2019). The onset of multimorbidity has been shown to occur 10 to 15 years later amongst people living in affluent areas compared to deprived areas, particularly when multimorbidity profiles include mental health disorders (Barnett et al., 2012). Compared to HICs, the burden of NCDs in LMICs is increasingly seen at younger ages, including in adolescents and young adults due to more behavioural and environmental risk factors, such as the consumption of ultra-processed foods in high volumes (Basto-Abreu et al., 2022).

Research conducted in South Africa demonstrates that understanding the relationship between age and co-occurring diseases requires an understanding of the socioeconomic conditions in which these individual-level factors unfold. For example, Chang et al. (2019) explains that the commonly observed positive relationship between multimorbidity and lower income-status and age are not observed in South Africa due to differentials in epidemiological profiles of subgroups. For example, poorer and younger groups have a higher prevalence of HIV and anaemia, while richer and older groups have a higher prevalence of cardiometabolic conditions (Chang et al., 2019). In South Africa, the odds of multimorbid physical conditions are higher in older participants, while physical-mental multimorbidity

is more common among participants younger than 45 years (Petersen et al., 2019). While these findings are significant to develop targeted interventions for different age groups, the authors note that age-related differences in disease profiles should not be understood without unpacking the socioeconomic factors, that may underscore these differences, such as the differences in housing stability between age groups (Petersen et al., 2019).

A similar approach should be applied to understanding the impact of gender and ethnicity on the co-occurrence of diseases. For instance, gender is an important determinant of individuals' multimorbidity profile in South Africa, as females living with multimorbidity are more at risk for depression, while males are more at risk for alcohol abuse (Petersen et al., 2019). Wade et al. (2021) demonstrates an increased risk of death in South African males living with HIV multimorbidity compared to patients living with multimorbid conditions excluding HIV, although this differentiation was not statistically significant in women. While differences in disease profiles may be linked to sex-related biological differences and histories of pregnancy in women, research needs to consider the various intersectional challenges in the social structures and processes of society that women face which affect their higher risk of depression as a part of their multimorbidity profile more compared to men (Moreno-Juste et al., 2023). This is especially important in South Africa where women face higher rates of unemployment, domestic violence, and lower educational levels than men (Statistics South Africa, 2013). This complexity is not accounted for when categorising research participants into female and male categories but should be considered when interpreting results (Weimann et al., 2016).

Similarly, ethnic differences in multimorbidity profiles cannot merely be considered from a biological point but should also consider the large differences in the socioeconomic determinants that may differ between groups (Weimann et al., 2016). The ethnic group-related differences in employment and educational opportunities in South Africa are especially important given the country's history of racial discrimination during Apartheid (Statistics South Africa, 2021). There are also cultural differences in risk factors between racial groups (such as diets and behavioural choices), although stereotypical risk factors may not apply to all individuals in a particular group or may vary between different areas in which the same racial groups reside (Weimann et al., 2016). Thus, the influence of biological factors of race and gender need to be analysed and interpreted with caution.

2.3.2. Household-level factors

A systematic review of studies conducted in North America, Europe and Australasia found that the odds of living with co-occurring diseases are 4.4 times higher in households with the lowest income level compared to the highest income level, while households in the most deprived geographical areas

have a higher prevalence of multimorbidity (Ingram et al., 2021). The authors highlight the importance of understanding the social determinants of co-occurring diseases between households in the same contexts and between households in different geographical contexts for effective policy interventions (Ingram et al., 2021).

In LMICs, a high burden of multimorbidity is seen at the household level for individuals living in the lowest socioeconomic stratum, including the high direct and indirect costs of covering healthcare services and the invisible non-remunerated costs of family members largely fulfilling the role of caregivers while foregoing other means of household income (Pesantes et al., 2017). However, research conducted in Jamaica demonstrates that the material circumstances of the household, including the housing conditions and physical features of the neighbourhood environment, were not significant predictors of co-occurring diseases (Craig et al., 2021). Petersen et al. (2019) found that in urban areas of South Africa, household food insecurity and poverty were associated with higher odds of co-occurring depression and alcohol use disorders among chronic disease patients, while Weimann et al. (2016) show that households in urban areas with high levels of household obesity were associated with higher odds of co-occurring physical diseases. The lack of consensus between different studies about the influence of the household level factors on the co-occurrence of physical and psychological disorders warrant further research inquiries to inform context-specific policies.

2.3.3. Contextual factors

The contextual factors in LMICs largely shape the occurrence, severity, and outcomes of physical and psychological multimorbidity, reinforcing factors that cause and perpetuate the poverty cycle (Basto-Abreu et al., 2022, Wade et al., 2021, Jaspers et al., 2015). This includes exposure to environmental risk factors, including pollution and poor nutrition; limited opportunities for engagement in preventive efforts such as physical activity; and weak social protection systems, whereby individuals are deterred from seeking healthcare due to the related expenditures (Swinburn et al., 2019).

The facilities where individuals seek healthcare in LMICs are also often poorly financed and lack effective screening and treatment options to timely diagnose and manage the co-occurrence of chronic diseases (Basto-Abreu et al., 2022). Poor continuity and integration of the management of co-occurring diseases translate into polypharmacy and multiple visits to multiple healthcare providers, which discourages patients from seeking care and contributes to early disease progression, premature morbidity, and high rates mortality in LMICs (Swinburn et al., 2019). A study in India highlights the importance of understanding the predictors of co-occurring diseases between different facility types, since the analysis showed that socioeconomic factors of education and income were larger

determinants of co-occurring diseases in private facilities, while individual factors of age, gender and ethnicity were larger determinants in public facilities (Pati et al., 2020).

A spatial analysis of multimorbidity in districts throughout South Africa revealed that socioeconomic disadvantage reflected the spatial pattern of multimorbidity in the country, with hotspots located in the Eastern Cape and KwaZulu-Natal provinces. There is a link between these hotspots and the histories of higher socioeconomic disadvantage in these areas since both provinces were predominately rural homelands during Apartheid which were reserved for Black African ethnic groups, and therefore, continue to face high levels of poverty and deprivation today (Weimann et al., 2016). The authors note that the district-level analysis may be too expansive to capture the spatial differences in socioeconomic status and multimorbidity and that further analyses are required to discern these spatial differences at a smaller spatial scale, such as at the intra-provincial, urban-rural, or intra-urban spatial level. It is therefore important to understand how these contextual factors may differ between different countries and between different contexts in the same country to effectively address the most imminent determinants on the co-occurrence of chronic diseases (Basto-Abreu et al., 2022, Pati et al., 2020). This understanding should extend beyond provincial analyses, to unpack the intra-provincial differences in the covariates of co-occurring diseases and support the development of such context-specific policies (Lund et al., 2010, Weimann et al., 2016).

To summarise, the research conducted in various contexts globally demonstrates that disease co-occurrence has substantial implications on resource allocation in health systems, and planning in LMICs should account for the fact that diseases do not occur in siloes. Moreover, the available research suggests that the covariates of co-occurring diseases extend beyond biological factors to include household-level and contextual factors, although these factors may differ between different contexts. The existing gaps in effective integrated management of co-occurring diseases in South Africa substantiates ongoing research in different contexts of the country to identify at-risk population groups, highlight the most crucial social determinants that need to be addressed, and inform context-specific policy development. There is an ongoing gap in the available literature on the covariates of co-occurring diseases in the Western Cape province of South Africa**.**

The current study makes use of the data collected by Project MIND which was conducted in the Western Cape province of South Africa. Project MIND started in 2014 with a study co-design between the Western Cape Department of Health (WCDoH), the South African Medical Research Council (SAMRC), the University of Cape Town, and Oxford University (Myers et al., 2018). The purpose of the project was to assess what the health system capacity and barriers are to integrating mental health

interventions into chronic disease services to develop acceptable and feasible care models (Myers et al., 2018). Project MIND included a three-arm, cluster randomised controlled trial used to test the effectiveness of two collaborative care models for integrated chronic disease and mental health care and to assess which of these models are the most effective and cost-effective for improving chronic disease and mental health outcomes (Myers et al., 2022). The data of the randomised control trial (enrolment between 1 May 2017 and 31 March 2019) is used in this study to determine the covariates of depression amongst patients living with HIV and/or diabetes in the Western Cape province of South Africa**.**

3. Research question

1. What are the predictors of depressive symptoms in patients living with HIV and/or diabetes at the baseline of Project MIND?
2. Are there differences in the depressive symptoms in the patients from different contexts (such as households and PHC study sites) at the baseline of Project MIND?

4. Aims and Objectives:

4.1. Aim of the study

This study aims to investigate the social determinants of depressive symptoms among patients living with HIV and/or diabetes at the hierarchical levels of individual, household, and community where patients receive chronic disease management.

4.2. Objectives

1. To examine the predictors of depressive symptoms in patients living with HIV and/or diabetes at the baseline of Project MIND.
2. To assess the variation in the baseline depressive symptoms in patients living with HIV and/or diabetes across households and PHC study sites of Project MIND.

5. Methods

5.1. Study design

The current study makes use of the data collected by Project MIND which was conducted in the Western Cape province of South Africa. Project MIND included a three-arm, cluster randomised controlled trial (Myers et al., 2022). The intervention was offered by health providers at the PHC clinics who screened patients during routine HIV or diabetes care for recent alcohol use (in the past year)

and low mood (in the past 2 weeks) and referred patients for further eligibility screening for the study by an assessor (Myers et al., 2022).

The randomised controlled trial of Project MIND is described below to add contextual depth to this research proposal.

5.1.1. Study setting

Project MIND was conducted in the Western Cape province of South Africa. The WCDoH purposively selected 24 PHC clinics which offered co-located HIV and diabetes services and treated enough patients to facilitate adequate recruitment (Myers et al., 2018). At the selected PHC clinics, these services were provided through separated and vertically organised clinics to prevent selection bias (Myers et al., 2018). The facilities varied in size and service comprehensiveness to ensure that the sample was representative of the variability of PHC facilities in the province, as well as of the provincial distribution of PHC clinics (including 15 urban and 9 rural sites) and the geographically distinct catchment areas and populations served in the different health districts (Myers et al., 2018).

5.1.2. Treatment randomisation

Randomisation was done at the PHC clinic level to avoid contamination, since Project MIND affected how healthcare services were provided at the clinics (Myers et al., 2022). A computer-generated sequence was used by an independent statistician to randomly assign clinics according to their urban–rural status stratification, to either a designated care group, a dedicated care group, or treatment as usual group, with eight clinics assigned to each treatment arm (Myers et al., 2022).

The eight treatments as usual clinics received standard care for mental health concerns, including advice on lifestyle choices, mood and alcohol use monitoring, and referrals to additional services as required (Myers et al., 2022). Through consultations with patients, providers, and stakeholders, the designated and dedicated intervention approaches of Project MIND were designed (Myers et al., 2022). The dedicated and designated approaches were implemented at eight clinics respectively (16 intervention clinics in total) and made use of identical interventions (Myers et al., 2022). However, the roles of the community health workers differed in each of the approaches (Myers et al., 2022). In the dedicated group, an additional community health worker was added to the chronic disease team, with the main task of delivering the MIND programme (Myers et al., 2022). In the designated group, a facility-based community health worker who was already a part of the chronic disease team was assigned to provide the MIND programme in addition to their responsibilities in the chronic disease team (Myers et al., 2022). The manualised MIND programme consisted of three intervention sessions

(45–60 minutes in duration) based on motivational interviewing and problem-solving therapy scheduled at least one week apart. The sessions focused on encouraging participants to engage in intervention and teaching strategies for coping with stress – a major risk factor for alcohol use disorders, depression, and poor chronic disease management (Myers et al., 2022).

5.1.3. Sample size and participants

The eligibility criteria included patients of at least 18 years old, who were taking medication for diabetes (Type 1 or Type 2) or antiretroviral therapy (ART) for HIV, who screened for depression (Center for Epidemiology Scale on Depression (CES-D) score ≥ 16) or for hazardous alcohol use (Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8) (Myers et al., 2018). The participants enrolled had not received treatment for a mental health condition or participated in any other study prior to or during enrolment (Myers et al., 2018).

The sample size of the randomised controlled trial of Project MIND was powered to detect reductions in risk of depression and harmful/hazardous alcohol use after 12 months. The sample size required to meet the inference requirements of the trial was calculated as eight clinics per arm (24 HIV and 24 diabetes services in total), with a cluster size of 25 participants per service (600 participants from HIV and 600 participants from diabetes clinics) (Myers et al., 2022). Participants were enrolled between 1 May 2017 and 31 March 2019 (Myers et al., 2022). After eligibility screening and the consent process, 1340 participants (801 with HIV; 622 with diabetes) were enrolled in the Project MIND study and participated in the baseline assessment (438 in the designated group (32.7%), 457 in the dedicated group (34.1%), and 445 (33.2%) in the treatment as usual group) (Myers et al., 2022).

5.2. Data collection

Enrolment in the randomised controlled trial of Project MIND occurred between 1 May 2017 and 31 March 2019. All activities involving the participants of Project MIND occurred in private spaces within the clinics (Myers et al., 2022). The patients who screened eligible for Project MIND study gave written informed consent for research participation prior to completing a computer-assisted assessment in either English, Afrikaans, or isiXhosa (the official languages of the province) of their baseline health characteristics (current chronic disease treatment, depression, and alcohol use), as well as their perceived health status and their self-reported socio-demographic information (age, education, relationship status, hunger frequency in the last month, and employment) (Myers et al., 2022).

Blood samples were taken for HIV viral load or HbA1c testing for diabetes was done and sent for analysis to a South African National Accreditation System-accredited laboratory (Myers et al., 2022).

1. HbA1c levels (for diabetes) were recorded as a continuous variable in Project MIND (Myers et al., 2018b). HbA1c is the traditionally used method to monitor glycaemic control and a good marker of chronic hyperglycaemia, the main characteristic of diabetes mellitus (Zemlin et al., 2015). The recommendations by the SEMDSA Guidelines for Diagnosis and Management of Type 2 Diabetes Mellitus for Primary Health Care (2009) and research on the diagnosis of prediabetes in the Western Cape province (Zemlin et al., 2015) is used in the current study to categorise HbA1c levels. These categories correspond with the standard cut-offs used in the Project MIND:
    a. Diabetes: HbA1c of 6.5% or higher.
    b. Normal: HbA1c of lower than 6.5%.
2. HIV-1 RNA viral load levels (for HIV) were recorded as a continuous variable in Project MIND (Myers et al., 2018b). The data is dichotomised in the current study according to standard cut-offs (Conan et al., 2022). These categories correspond with the standard cut-offs used in Project MIND:
    a. Normal viral load < 1000 copies/ul
    b. Abnormal viral load > 1000 copies/ul

For more information regarding the treatment arms and the outcomes of the trial, the full protocol of Project MIND (Myers et al., 2018) and the published research paper (Myers et al., 2022) can be consulted.

The interest of the current study is the data collected at the baseline assessment of Project MIND, prior to the intervention exposure. The current study employs a cross-sectional, quantitative analysis of the predictors of co-morbid depression among the patients living with diabetes and/or HIV included in the Project MIND baseline assessment. The current study makes use of the data collected from patients at the baseline assessment of Project MIND. All participants who screened for depressive symptoms, irrespective of their alcohol use screening results, will be included in this analysis.

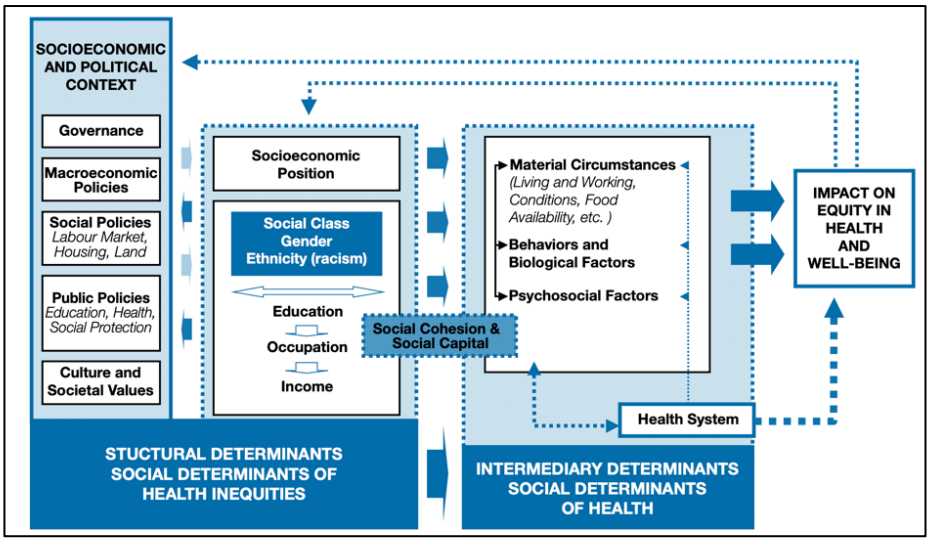
5.3. Conceptual framework

5.3.1. Commission on Social Determinants of Health (CSDH) model

The current study draws on the Commission on Social Determinants of Health (CSDH) model to unpack the predictors of depressive symptoms among chronic disease patients. This model has been useful to examine the determinants of health, illness and multimorbidity in previous research conducted in

South Africa (Alaba and Chola, 2013). The CSDH points to the importance of understanding health and illness as social processes and consequences. The CSDH model appreciates how social, economic, and political mechanisms influence the socioeconomic positions of population groups, and that these factors stratify groups according to income, education, occupation, gender, and ethnicity (Solar and Irwin, 2010). People's socioeconomic positions then shape the determinants of their health status and their access to healthcare, meaning that based on individuals' social status, they experience differences in exposure and vulnerability to illness and disability (Solar and Irwin, 2010). Thus, the model posits that there are multiple other factors outside of personal genetics that affect the occurrence and severity of diseases, including environmental, behavioural lifestyle, and socioeconomic factors (Solar and Irwin, 2010). The experience of illness then influences an individual's social position, for example affecting the operation of social, economic, and political institutions (Solar and Irwin, 2010).

Figure 1: CSDH conceptual framework (Solar and Irwin, 2010, pp:6)



The CSDH model highlights the importance of addressing structural and intermediary determinants of health to create an enabling environment for equitable healthcare delivery and improve health outcomes (Solar and Irwin, 2010). These determinants are crucial for policies and research to address both the social factors that influence the health of populations (i.e., the determinants of health) and the social processes that cause and maintain the unequal distribution of social factors between different groups occupying unequal societal positions (i.e., the determinants of the inequalities of health) (Solar and Irwin, 2010). In the current study, these determinants are defined according to the CSDH framework (Solar and Irwin, 2010):

1. Structural determinants refer to the "interplay between the socioeconomic-political context, structural mechanisms generating social stratification and the resulting socioeconomic position of individuals" (pp: 28) or the social determinants of health inequities (Solar and Irwin, 2010). These factors create or reinforce social stratification or class differences in society, and thereby, define individuals' socioeconomic positions within the societal hierarchies of power and access (Solar and Irwin, 2010). The most significant structural determinants and proxy indicators include income, education, occupation, social class, gender, and race/ethnicity (Solar and Irwin, 2010).

2. Intermediary determinants are influenced by the configuration of underlying social stratification which define the differences in illness exposure or vulnerability (Solar and Irwin, 2010). Genetic and biological processes are included as the factors that mediate the personal effects of the social determinants of health (Solar and Irwin, 2010). The main categories of intermediary determinants of health include (Solar and Irwin, 2010):
    a. Material circumstances (including the physical and natural conditions of living and consumption potential).
    b. Psychosocial circumstances (including life stressors, stressful living circumstances and level of social support and coping styles).
    c. Behavioural and/or biological factors (including smoking, alcohol consumption, diet, physical exercise, sex, and age).
    d. Health system factors (including geographical access, affordability, and patient empowerment).

5.4. Selection of variables

The variables used in the current study are chosen based on their availability in the dataset and their relevance in literature on the predictors and covariates of co-morbid depression among patients living with HIV and/or diabetes.

5.4.1. Dependent variable

The outcome variable of the current study is depressive symptoms among patients living with diabetes and/or HIV. In the Project MIND baseline assessment, depressive symptoms were measured by a 20-item Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D measures patients' depressive behaviours and feelings during the previous week on a four-point Likert scale, ranging from 0 (no symptoms) to 3 (symptoms present most of the time) (Radloff, 1977). The composite scores on

the CES-D range from 0 to 60, with higher scores indicating more severe symptoms of depression (Radloff, 1977). A CES-D score ≥ 16 indicates when depressive symptoms are clinically relevant, and this standard cut-off score has yielded acceptable sensitivity and specificity estimates in previous research (Naughton and Wiklund, 1993, Moon et al., 2017).

The current study uses data for participants captured in the Project MIND baseline assessment. The dependent variable of this study is a binary categorical variable of participants' depressive symptoms indicating: (1) no to mild depressive symptoms (CES-D score < 16) and (2) moderate to severe depressive symptoms (CES-D score ≥ 16).

5.4.2. Independent variables

The independent variables of the current study include individual-level demographic variables, household characteristics and PHC site information as captured in the Project MIND baseline assessment. The following variables are classified as structural or intermediary determinants according to the CSDH conceptual framework (Solar and Irwin, 2010):

Structural determinants

1. Race
2. Education
3. Occupation
4. Income

Intermediary determinants

1. Biological factors:
    a. Age
    b. Sex

2. Behavioural factors:
    a. Smoking
    b. Obesity
    c. Hazardous/harmful alcohol use
    d. General self-efficacy
    e. Self-reported adherence > 90%

3. Material circumstances:
    a. Average household expenditure
    b. Household food insecurity
    c. Housing stability

4. Psychosocial factors:
    a. Relationship status: self-reported relationship status was dichotomised as single (including widow/widower, divorced, or separated, and never married) and not single (including married and living with partner).

    b. Social support: Measured using the 19-item Medical Outcomes Study (MOS) Social Support Survey scale (Sherbourne and Stewart, 1991) in the Project MIND baseline assessment, including the four aspects social support (tangible, affectionate, positive social interaction, and emotional/informational support). The items are scored between 1-5, and composite scores are created (between 0-100), with 0 indicating the lowest level of social support (Sherbourne and Stewart, 1991). In the current study, this variable is included as a continuous variable, with a higher score indicating a higher level of social support.

    c. Social problem-solving: The Social Problem-Solving Inventory-Revised: Short Form (25-item self-report questionnaire) was used in the Project Mind baseline assessment to determine participants' functional problem-solving skills. Higher scores in the Negative problem orientation, Impulsivity-carelessness style and Avoidant style on the Social Problem-Solving Inventory reflect a more maladaptive approach to problem solving (Hawkins et al., 2009). Higher scores on the Positive problem orientation and Rational problem solving on the Social Problem-Solving Inventory indicate more adaptive problem solving (Hawkins et al., 2009). In the current study, this variable is included as a categorical variable (see appendix B).

5. Health system factors
    a. Area of PHC clinic (urban or rural)

5.5. Data analysis

Descriptive analysis will be conducted to summarise the quantitative and qualitative variables. Participants' baseline characteristics will be summarised using mean (n) and standard deviation (SD)

for continuous variables and frequency (n) and percentage (%) for categorical variables. The baseline characteristics table of the participants separated into the overall sample, participants living with HIV and depressive symptoms, participants with diabetes and depressive symptoms, and participants living with HIV and diabetes and depressive symptoms (see appendix A and B).

5.5.1. Multi-level analysis

To address the first and second objective***s*** of the study, multi-level analysis will be used. The randomisation and sample design of Project MIND was performed in a two-stage manner that, firstly, a number of PHC clinics were sampled, and secondly, within each of the sampled PHC clinics, a sample of participants were drawn (Myers et al., 2018). Thus, the dataset is hierarchical by nature with sampled units at two levels. Moreover, individuals are nested within households with different characteristics.

Multi-level analysis is a useful tool to analyse data drawn from different levels and will support an analysis of depressive symptoms as it relates to individual characteristics, such as age and income, as well as to contextual characteristics, such as the household and/or the PHC clinics where they receive healthcare. Based on the CSDH framework, the difference between an individual's health and the population average can be attributable to the differences in their contextual realities, in part, as well as to the individual differences within different contexts. There may be common contextual factors that influence the depressive symptoms of multiple individuals in the same PHC catchment areas which are not shared by individuals from other areas (Leyland and Groenewegen, 2020). In this analysis, there is consideration of how variations in the context in which people with chronic diseases live can impact variances in their health outcomes.

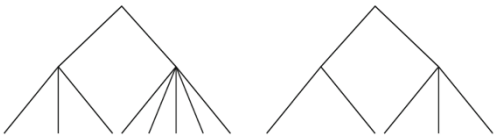
In the case of depressive symptoms among patients living with HIV and/or diabetes, a multi-level regression analysis will allow partitioning this variation of depressive symptoms into factors which are attributable to the context of the PHC facility (such as access to healthcare services), to the household context (such as income and wealth quintile), and to the factors which are attributable to the individual (such as age, gender, and education), and hence quantify the importance of these different levels on the variance of depressive symptoms (Leyland and Groenewegen, 2020). By including all three levels in the analysis, this study will better understand the complex relationships between these factors and depressive symptoms, and account for the variation that may exist at each level. For example, individual-level factors may be more strongly associated with depressive symptoms among patients living with HIV, while household-level factors may be more important for those with diabetes. Additionally, site-level factors such as cost of accessing services may play a role in both groups. Overall,

this type of analysis will support recommendations for targeted policy interventions at the different levels to improve health outcomes in these populations.

This multi-level analysis will use a three-level pyramid structure with chronic disease patients with depressive symptoms at the lowest level (level one), nested within the household-level (level two), nested within the PHC catchment areas at the highest level (level three). The patient level (level one) is where the outcome (depressive symptoms) was measured at the baseline assessment of Project MIND and will be analysed in the regression without individual level (level one) covariates, as well as with individual level covariates.

Figure 2: Proposed multi-level hierarchy

PHC catchment area (3)
Households in SES strata (2)
Individual patient (1)



(Leyland and Groenewegen, 2020, pp:50)

The household level (level two) will be included in the regression analysis using household-level variables. Household-level variables will be added in the analysis upon inspection of the available data. The second level will allow for insight into the within-PHC area variance of depressive symptoms according to the variance between households.

The PHC site level (level three) will be included in the regression analysis using PHC-level variables. PHC-level variables will be added in the analysis upon inspection of the available data. Each site/district will be analysed in comparison to all other sites/districts included in Project MIND. This level will allow for insight into the between-PHC area variance of depressive symptoms, which is likely to occur given the wide geographical variance of the PHC sites included in Project MIND.

It is expected that level three of the analysis will show the contextual phenomenon of co-occurring diseases by demonstrating to what extent health differences among people are attributable to the communities in which they reside (Merlo et al., 2005). Examining the variation in depressive symptoms across different sites/districts can help identify disparities in the quality of care and support services provided to patients living with HIV and/or diabetes. This information can be used to inform policies and interventions aimed at reducing these disparities and improving the overall quality of care.

The regression formula for multi-level analysis of depressive symptoms among patients living with diabetes and/or HIV at the individual, household, and PHC site level can be expressed as follows:

$$Depressive\ symptoms = \beta 0 + \beta 1 * Individual\ predictors + \beta 2 * Household\ predictors + \beta 3 * PHC\ predictors + \varepsilon$$

where:

- β0 represents the intercept or the average level of depressive symptoms across all participants.
- β1, β2, and β3 represent the effects of the individual-level, household-level, and PHC-level predictors on depressive symptoms, respectively
- ε represents the error term as the sum of the residual at the individual-level, household-level, and PHC-level

For each level predictor, the regression formulas can be expressed as follows:

$$Individual\ predictor\ (\text{Level } 1) = \gamma 00 + \gamma 01 * Individual\ covariates + u0i$$

where:

- γ00 represents the intercept for the individual-level predictor.
- γ01 represents the effect of the individual-level covariates on the individual-level predictor.
- u0i represents the random effect for the individual-level predictor.

$$Household\ predictor\ (Level\ 2) = \gamma 10 + \gamma 11 * Household\ covariates + u1j$$

where:

- γ10 represents the intercept for the household-level predictor.
- γ11 represents the effect of the household-level covariates on the household-level predictor.
- u1j represents the random effect for the household-level predictor.

$$PHC\ predictor\ (Level\ 3) = \gamma 20 + \gamma 21 * PHC\ covariates + u2k$$

where:

- γ20 represents the intercept for the PHC-level predictor.
- γ21 represents the effect of the PHC-level covariates (including socioeconomic stratum) on the PHC clinic-level predictor.
- u2k represents the random effect for the PHC-level predictor.

The multi-level regression formula accounts for the hierarchical structure of the data, with individual-level predictors nested within households and households nested within healthcare clinics. The random effects (u0i, u1j, and u2k) represent the variability in the intercepts across the different levels of analysis, which allows for modeling of the between-group differences.

A common pitfall of multi-level analysis is not accounting for confounding variables, which introduces bias to the results. Contextual level factors may display confounding either (1) within-level (i.e., confounding by other contextual factors); (2) cross-level (confounding by individual characteristics); or (3) by confounding the relationship between an individual-level variable and the outcome (Leyland and Groenewegen, 2020). Confounding variables will be adjusted in the analysis to mediate this effect.

Intra-class correlation will be used to measure the variation in depressive symptoms attributed to the PHC area and household-level respectively. The results for the multi-level regression analysis will be presented as partial regression coefficients together with the respective 95% confidence intervals (Cis) of each to signify precision.

5.5.2. Dealing with missing data

A census will be used in the current study to include all the available data of the study population collected during the baseline assessment of Project MIND. The extent of missing data will be assessed prior to the planned analyses. Missing data will be treated as missing at random and no imputation will be performed in the following circumstance as recommended by Jakobsen et al. (2017):

1. Complete case analysis will be used if the proportions of missing data are below approximately 5% and if it is implausible that the missing data is characteristic of one group (missing not at random). In this case, the impact of missing data will be regarded as negligible and will be ignored in the analysis (Jakobsen et al., 2017).
2. Complete case analysis will be used if only the dependent variable has missing values and no auxiliary variables can be identified (auxiliary variable referring to “variables not included in the regression analysis but correlated with a variable with missing values and/or related to its missingness” (Jakobsen et al., 2017, pp:3). In this case, no imputation will be required.
3. Complete case analysis will be done if it is relatively certain that the data are missing completely at random, which can be confirmed by with Little’s test (Jakobsen et al., 2017).

Missing data will be imputed in the following circumstance as recommended by Jakobsen et al. (2017), if large proportions (>40%) of data are missing, or if the missing at random assumption seems implausible since this might mean that the results of the analysis will be at risk of incomplete outcome

data bias. Multiple imputation – a simulation-based statistical technique – will be used to handle missing data, including the following three steps (Jakobsen et al., 2017):

1. Imputation step: multiple imputation includes multiple sets of values for missing data, to replace the data that is missing with a random sample of plausible values. An imputation model will generate multiple completed datasets. Fifty imputed datasets have been suggested to reduce sampling variability from the imputation process (Jakobsen et al., 2017).
2. Completed-data analysis step: A separate analysis is performed for each dataset generated during the first step (Jakobsen et al., 2017), i.e., 50 results are constructed.
3. Pooling step: A combination of the results from the completed-data analyses (step 2) will be used to create a single multiple-imputation result (Jakobsen et al., 2017).

All the analyses will be done with Stata version 15 for MacOS.

6. Ethical Considerations

6.1. Ethical approval

This protocol will be submitted to the University of Cape Town's Human Research and Ethics Committee (HREC) for ethical approval. Ethics approval for Project MIND was granted by The South African Medical Research Council, Cape Town, South Africa (EC004–2/2015), the University of Cape Town, Cape Town, South Africa (089/2015), and Oxford University, Oxford, UK (OxTREC_2–17) (Myers et al., 2022).

6.2. Confidentiality and Privacy

The data used in the current study has been anonymised during the Project MIND data collection and will be kept in a password protected online platform to which only the necessary members of the research team (i.e., the student and supervisor) will have access. The published data will be described in aggregates, will remain de-identified, and will maintain participant anonymity.

6.3. Publication and Dissemination Policy

The dissertation will be submitted in accordance with the requirements of the Health Economics track of the Master's in Public Health degree. The findings of the current study will be relevant to stakeholders particularly within the WCDoH and other researchers. Therefore, an article will be prepared for submission to a peer-reviewed journal which is yet to be specified. A policy brief will also be prepared to disseminate the findings to relevant policymakers.

6.4. Budget

Project MIND was funded British Medical Research Council, Wellcome Trust, UK Department for International Development, the Economic and Social Research Council, and the Global Challenges Research Fund (Myers et al., 2022). The current study will not benefit from the funding made available to Project MIND. No significant further costs are anticipated for the current study, and the dissertation will be self-funded (appendix C). The principal researcher declares no conflict of interest.

6.5. Logistics

The current study will be carried out over 12 months (1 year), as demonstrated in appendix D.

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Part B: Structured Literature Review

1. Introduction

This literature review aims to highlight the available research on the determinants of co-occurring diseases globally and in South Africa, with a specific focus on depressive symptoms among patients living with chronic health conditions, including HIV and/or diabetes. This review includes literature that demonstrates how health determinants are not only situated at the level of the individual but are intricately linked to the contextual factors at the household and community levels – a notion supported by the Commission on Social Determinants of Health (CSDH) model. The literature shows that effective policymaking to address the social determinants of co-occurring diseases depends on contextually relevant information, which substantiates the need for further inquiry into co-occurring mental and physical health conditions in the Western Cape province of South Africa. Finally, a methodological review highlights that multi-level modelling is an appropriate research method to unpack the influence of contextual factors on co-occurring health conditions.

2. Search strategy

An online literature search was conducted on PubMed Central, MEDLINE, Web of Science, PsycINFO, and CINAHL electronic databases up to 30 July 2023. In addition, a similar search was conducted on Google, Google Scholar, and on Africa Journals Online making use of the same search algorithm used in the electronic database search. The search was altered according to the specifications of the search engines used. Furthermore, the reference lists of research papers identified as relevant in the electronic search were screened to identify relevant literature. The search terms included "physical and mental health multimorbidity" and other versions such as "physical and mental illness co-occurrence", "co-morbid physical and mental health conditions", and "co-occurring physical and mental health conditions". The search was also conducted using terms related to the physical and mental health conditions addressed in this study, including "co-morbid HIV and diabetes", "co-morbid HIV and depression", and "co-morbid diabetes and depression". Other search terms included "socioeconomic determinants of health", "social determinants of health", "socioeconomic correlates", and "socioeconomic predictors". The search was further refined to identify contextually appropriate research by including search terms such as "low-income and middle-income countries", "low- and middle-income country", "LMIC", "deprived country", "deprived population", "developing country", "developing economy", "developing nation", "poor country", "poor economy", "poor nation", "poor population", "third world country", or "transitional country". South African research was identified by adding search terms including "Sub-Saharan Africa" and "South Africa". Date and

language search filters were added to include research from the year 2000 to the date of the electronic search, and to restrict the retrieval of articles to the English language.

3. Background

The co-occurrence of health conditions is a concern for health systems globally, as approximately one-third of the adult population in low-income and middle-income countries (LMICs) live with two or more health conditions (Nguyen et al., 2019). Co-occurring diseases increase the risks of mortality and morbidity, reduce quality of life, productivity, and increase healthcare utilisation and expenditure (Arokiasamy et al., 2015, Bähler et al., 2015, Oni and Unwin, 2015, Salisbury et al., 2011, Glynn et al., 2011, Gijsen et al., 2001). The steady increase in global life expectancy is likely to result in a higher population prevalence of co-occurring diseases, inevitably creating higher burdens on health systems in the future (Xu et al., 2017). While there is extensive research on co-occurring diseases in high-income countries (HICs), it is sparse in LMICs and there is a need for further studies in LMICs to inform policy development, healthcare resource allocation, and effective clinical management (WHO, 2022a). Generating knowledge on this topic in LMICs is relevant since vulnerable populations in lower socioeconomic settings are especially at risk of experiencing co-occurring diseases and face increased socioeconomic hardships that underscore poor health outcomes amongst individuals with more than one health condition (Xu et al., 2017).

Research on co-occurring diseases is crucial in South Africa as the disease burden and social determinants of health differ significantly from HICs and other LMICs (Roomaney et al., 2021). South Africa faces a unique quadruple disease burden, including a high prevalence of communicable diseases such as HIV and tuberculosis; a growing rate of non-communicable diseases such as diabetes and hypertension; high rates of deaths from injuries and violence; and highly prevalent neonatal, child, and maternal mortality (The Presidency of the Republic of South Africa, 2014). The distribution of this disease burden in South Africa is historically inequitable, with disparities between private and public healthcare sectors, rural and urban areas, different provinces, and regions within provinces (Rispel, 2016, Downie and Angelo, 2015). The unique nature of disease burden necessitates context-specific knowledge and substantiates ongoing research into co-occurring diseases within the country's specific socioeconomic and contextual circumstances (Roomaney et al., 2021).

Morbidity and mortality resulting from the co-occurrence of chronic physical and mental health conditions pose challenges to healthcare systems worldwide, given the limited capacity of health systems to integrate the management of various chronic diseases with mental healthcare (Mahomed

et al., 2014). The prevalence of mental health disorders is growing, and a significant treatment gap exists between provinces in South Africa (Lund et al., 2010, Bantjes et al., 2019). Moreover, the management of depression alongside frequently associated chronic physical conditions, such as HIV and diabetes, is complex in the South African context (Department of Health South Africa, 2021).

To generate a deeper understanding of co-occurring depression, HIV, and diabetes in South Africa, research that focuses on the multifaceted contexts in which these conditions unfold is required (Lund et al., 2010). Ongoing research is also required to identify the significant socioeconomic determinants of these co-occurring diseases, as well as vulnerable groups, to inform effective policy responses in different provinces in South Africa (Bernard et al., 2017, Abas et al., 2014, Leone et al., 2012).

4. Global burden of disease

The World Health Organisation highlights that the main drivers of life expectancy and healthy life expectancy (HALE) are global inequalities in mortality and morbidity profiles (WHO, 2022c). While life expectancy has increased across all country income groups from 66.8 to 73.3 years (between 2000 and 2019), life expectancy remains higher in HICs compared to LMICs (WHO, 2022c). A global epidemiological shift, marked by changes in population age distribution, life expectancy, fertility, mortality, and morbidity, has led to an increased burden of non-communicable diseases (NCDs) (McKeown, 2009). Some theories, such as the *Theory of Epidemiologic Transition,* explain this shifting pattern as one whereby infectious diseases are gradually displaced by lifestyle diseases over time (Omran, 1971). This traditional notion has been replaced by a more nuanced understanding that global health patterns are intricate, dynamic, and influenced by multiple factors, including demographic, environmental, socioeconomic, and technological changes (Ciccacci et al., 2020). The interplay of various health determinants across different countries and contexts shapes the continuously evolving epidemiological profile to differentially affect the health of various population groups (McKeown, 2009). To effectively address the health system challenges associated with a growing global population and respond to the complex epidemiological transition, it is crucial to understand the main components of the global health burden. Currently, the major contributors to the global burden of disease include communicable and non-communicable diseases, along with mental health disorders (WHO, 2022a). This section provides a brief overview of these key contributors.

4.1. Communicable diseases

Communicable diseases refer to infectious diseases which are caused by the direct or indirect spread of micro-organisms, including bacteria, viruses, and parasites, between people, through insect or

animal bites, or through the ingestion of contaminated food or water (Barreto et al., 2006). Communicable diseases continue to constitute a double burden on population health in LMICs (Basto-Abreu et al., 2022). While the global investments in communicable disease programmes, especially HIV, tuberculosis (TB) and malaria, have lowered the mortality linked to these diseases from 30.7% to 18.4% (between 2000 and 2019), they remain the cause for approximately half of all deaths (46.8%) in LMICs (WHO, 2022c). HIV remains the fifth leading cause of DALYs lost (Murray et al., 2012) and sixth leading cause of mortality (Lozano et al., 2012). Communicable diseases significantly affect health outcomes when co-occurring with NCDs, and this burden predominantly falls on vulnerable health systems in LMICs (WHO, 2022a). Oni and Unwin (2015) highlight that addressing the global health burden requires an understanding of the complex interactions between communicable diseases and NCDs. Moreover, attention is required to the shared risk factors that mediate this co-existence of communicable diseases and NCDs to effectively combat the associated poor health outcomes (Oni and Unwin, 2015).

4.2. Non-communicable diseases

Non-communicable diseases (NCDs) refer to chronic diseases which "tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioural factors" (WHO, 2022b). NCDs are the leading cause of global mortality, including cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes (WHO, 2022b). NCD-related deaths account for over 85% of disease mortality in HICs (WHO, 2022c). The rise of NCDs pose challenges to the vulnerable health systems of LMICs, which vary in their preparedness to address the associated mortality, morbidity, and economic burden of the NCD burden (UNHLM, 2014, Ganju et al., 2020).

Global action plans, such as the WHO's 25 × 25 goal, aim to reduce premature NCD-related mortality by 25% by 2025 through addressing major risk factors (WHO, 2013). However, these strategies have shortcomings, including the exclusion of socioeconomic factors as NCD risk factors and the neglect of mental health despite its significant association with NCD-related mortality (Pryor et al., 2017, UNHLM, 2014, Whiteford et al., 2013). The United Nations High Level Meeting also emphasises that different countries face different challenges to adequately respond to the growing NCD burden, which cannot be addressed through one-size-fits-all approaches (UNHLM, 2014). To effectively respond to the growing impact of NCDs, there is a need for focused, collaborative approaches that consider the contextual realities of different countries and different regions within countries, as well as recognise the complex relationship between communicable diseases, NCDs, and mental health (Ganju et al., 2020, Pryor et al., 2017).

4.3. Mental health disorders

Mental health disorders are defined as disturbances in behaviour, cognition, or emotional regulation, causing distress and functional impairment (WHO, 2022a). Mental health disorders are in the top three most frequently occurring health conditions globally, affecting over a quarter of the population throughout their lifetime (WHO, 2022c). Mental health conditions accounted for 7.4% of DALYs (183.9 million) worldwide in 2010 (Daré et al., 2019), although the impact of mental health conditions have more recently been estimated as 13.0% of DALYs and 32.4% of Years Lived with Disability (YLDs) (Vigo et al., 2016). Whilst LMICs have an increasing prevalence of mental health disorders, these health systems remain focused on combatting communicable disease and non-communicable diseases (WHO, 2015).

Estimating the prevalence of mental health disorders is challenging, since deaths attributable to mental health conditions are often reported as physical problems (Daré et al., 2019, Whiteford et al., 2013). The lack of accurate prevalence estimations, coupled with stigma, diagnostic complexity, and underfunding of mental health services, hinder the inclusion of mental health prevention strategies in global chronic physical disease management (Pryor et al., 2017). This is concerning because, although mental health disorders in themselves are highly debilitating, the impact of mental illness is more severe when co-occurring with physical illnesses (Pryor et al., 2017). For example, while people suffering from a mental health disorder are more likely to have a chronic physical disease, they are also more likely to have worsened physical health outcomes, receive inferior care for their physical health problems, and have poor adherence to chronic physical disease medication (Al-Hayek et al., 2012, Daré et al., 2019, Arokiasamy et al., 2015). Considering mental health as it co-occurs with physical health condition is therefore crucial to effectively address its complexities effectively (Daré et al., 2019, Pryor et al., 2017).

5. Burden of disease in South Africa

The burden of disease in South Africa also reflects the epidemiological transition. South Africa – an upper middle-income country – is in a *protracted epidemiologic transition*, as the country is faced with dual burdens of infectious diseases and NCDs (Remais et al., 2013). The percentage of deaths from non-communicable diseases was lower than that of communicable diseases in 2003 (Statistics South Africa, 2017). However, since 2004, the deaths from communicable diseases surpassed those from NCDs, and this gap continued to widen after 2010 (Statistics South Africa, 2017). These changes in the causes of death and disease may overstretch the already strained health system, emphasising the development of novel responses to the evolving disease burden (Statistics South Africa, 2017, Remais

et al., 2013). This section demonstrates the impact of communicable diseases, NCDs and mental health conditions in South Africa.

5.1. Communicable diseases in South Africa

In South Africa, infectious and parasitic diseases accounted for 17.6% of all deaths in 2017 (Statistics South Africa, 2017). The country is currently at the centre of the HIV pandemic, with over 19% of adults aged 15 to 49 living with HIV (Allinder and Fleischman, 2019). The HIV burden continues to grow, with an estimated 270,000 new infections annually (Allinder and Fleischman, 2019). HIV prevalence varies significantly between gender and age groups, as well as across provinces (UNAIDS, 2019, South African National AIDS Council, 2016). Vulnerable population groups in South Africa include adolescent girls and young women, female sex workers, men who have sex with men, people who inject drugs, and transgender individuals (Haffejee et al., 2023, Cloete et al., 2019). The high burden of tuberculosis (TB) exacerbates the prevalence rates of HIV in South Africa, with 63% of people living with TB also having HIV (South African National AIDS Council, 2016).

South Africa has made progress in reducing new HIV infections (declined from 360 000 to 270 000 between 2012 and 2016) (South African National AIDS Council, 2016), which can be partly attributed to the increased governmental investments in combatting communicable diseases and the move away from relying solely on donor-funded programs (Allinder and Fleischman, 2019). The National Strategic Plan on HIV, TB, and STIs (NSP) 2017-2022 emphasises that multi-sectoral partnerships and context-specific plans should address the needs of different provinces, districts, and population groups in a decentralised manner (South African National AIDS Council, 2016). However, these interventions and scale-up of investments have not been sufficient to combat the ever-growing prevalence of communicable diseases (Allinder and Fleischman, 2019), as the underlying factors that perpetuate these diseases have been neglected in prevention strategies (Haffejee et al., 2023). These factors include the poor living conditions, unsafe drinking water and limited food security (UNAIDS, 2019, WHO, 2022c), widespread poverty, unemployment, and limited education beyond primary school level and disease-related knowledge (Haffejee et al., 2016), cultural norms and accepted sexual practices (Saasa et al., 2018), high rates of teenage pregnancy, sexually transmitted infections (STIs), and interpersonal and gender-based violence (Hallman, 2005, UNAIDS, 2019). Thus, the social conditions in which communicable diseases unfold in South Africa require further research attention to support effective policy interventions beyond merely curing the symptoms of disease (Haffejee et al., 2023, Hallman, 2005).

5.2. Non-communicable diseases in South Africa

NCDs significantly contribute to the disease burden in South Africa, accounting for approximately 37% of mortality and 16% of disability-adjusted life years (DALYs) (Maimela et al., 2016). The country faces a high prevalence of the big 5 NCDs, including cardiovascular diseases, cancer, type 2 diabetes mellitus, respiratory illnesses, and mental health disorders (Samodien et al., 2021). NCDs do not unfold in singularity in South Africa; rather, the progression of disease is embedded in the country's social and economic disparities (Samodien et al., 2021, Maimela et al., 2016). Addressing NCDs in South Africa necessitates tackling the socio-economic factors that exacerbate NCD incidence and severity (Scott et al., 2017).

An NCD of increasing concern is diabetes in South Africa and in LMICs, as diabetes-related mortality has increased by 13% between 1980 and 2014 (WHO, 2023). South Africa has witnessed a rapid rise in diabetes prevalence, from 9% in 2015 to 11.3% in 2021, which is the highest prevalence in Africa (International Diabetes Federation, 2021). This is while an estimated 45.4% of diabetics in South Africa remain undiagnosed (International Diabetes Federation, 2021). The diabetes-related health expenditure in South Africa has grown to an estimated total of USD7.2 billion (International Diabetes Federation, 2021).

The South African National Department of Health (NDoH) has established specific units of NCD prevention and management, as well as various NCD policies (Puoane et al., 2017). Notably, in 2011, a summit on NCDs led to the development of the *Strategic plan for the prevention and control of non-communicable diseases 2013–2017* which focuses on NCD prevention (Puoane et al., 2017). Other policies include the *National Health Promotion Strategy and Policy 2015–2019*, the *Liquor Act of 2003*, the *Tobacco Product Control Act* (last amended in 2016), *The Strategy to Prevent and Control Obesity 2015–2020*, and the *National Food and Nutrition Security Policy* (Puoane et al., 2017). To move from these policies on paper to implementation, the Primary Health Care (PHC) system with Ward-based Outreach Teams (WBOTs) have been able to deliver integrated NCD services in the community (Puoane et al., 2017). However, ongoing research is necessary to optimise NCD prevention and control efforts in South Africa especially since the health burden, available services, and specific needs of different provinces differ (Puoane et al., 2017).

5.3. Mental health in South Africa

In South Africa, 38.5% of respondents in a study reported at least one lifetime common mental disorders (anxiety, mood and substance use disorders), the most common being major depressive disorder (24.7%) (Bantjes et al., 2019). In South Africa, over a quarter of adults report moderate to

severe symptoms of probable depression (Craig et al., 2022). Depression severity varies between different provinces and access to services, according to levels of household poverty, and across several socio-demographic determinants, including age, marital status, education level, and living circumstances (Craig et al., 2022). Unfortunately, the treatment gap for mental health disorders in South Africa remains severe, as only one in four people receive appropriate treatment (Lund et al., 2010), and only 0.89% of the uninsured population with mental healthcare needs receive public outpatient and inpatient mental healthcare (Docrat et al., 2019).

While critical steps have been taken in mental health policy reforms in South Africa, including the *Mental Health Care Act 17 of 2002*, the *National Health Insurance Policy of 2017*, and the *South African National Mental Health Policy Framework and Strategic Plan 2013–2020*, the mental healthcare budget and service delivery have not actualised the policy ideals and still represent significant disparities between provinces (Docrat et al., 2019). Variations in mental health prevalence and outcomes across South African provinces are influenced by unequal resource availability and socio-economic determinants, such as poverty and unemployment (Craig et al., 2022, Lund et al., 2010). Planning for mental healthcare requires ongoing context-specific data to ensure interventions are tailored to the unique needs of provinces and areas within them (Craig et al., 2022, Lund et al., 2010).

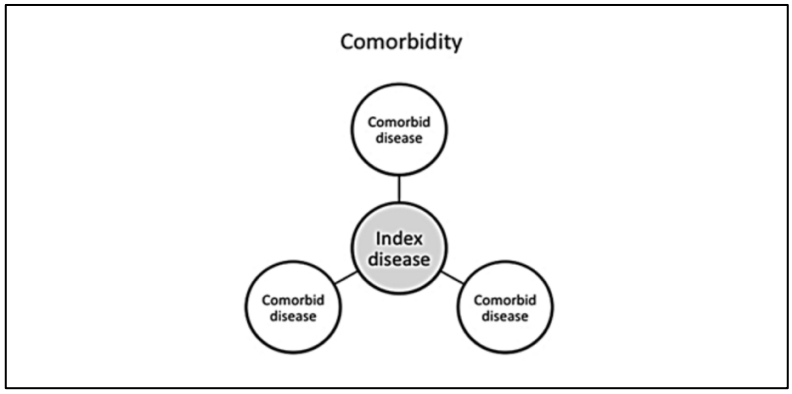
6. Co-occurring diseases

The evidence discussed up to this point highlights the severity and complexity of communicable diseases, NCDs, and mental health disorders as they occur respectively in the South African context. Increasingly, there is recognition that these diseases do not occur in siloes, but that the co-occurrence of these diseases pose a significant threat to the sustainability and responsiveness of health systems globally (WHO, 2022a, Thienemann et al., 2019, WHO, 2015, Arokiasamy et al., 2015). The following section offers a theoretical review and explores the prevalence of co-occurring diseases globally and in South Africa to untangle its complexity and highlight the need for further context-specific data to support health system planning.

6.1. Defining co-occurring diseases and implications for management

Comorbidity denotes the presence of clinical conditions that concurrently coexist or have the potential to arise during the trajectory of an individual's primary illness (Boyd and Fortin, 2010). Typically examined and managed through the lens of a central index disease, this approach engenders disjointed treatment regimens for each distinct co-morbid illness, as depicted in *Figure 1* (Boyd and Fortin, 2010).

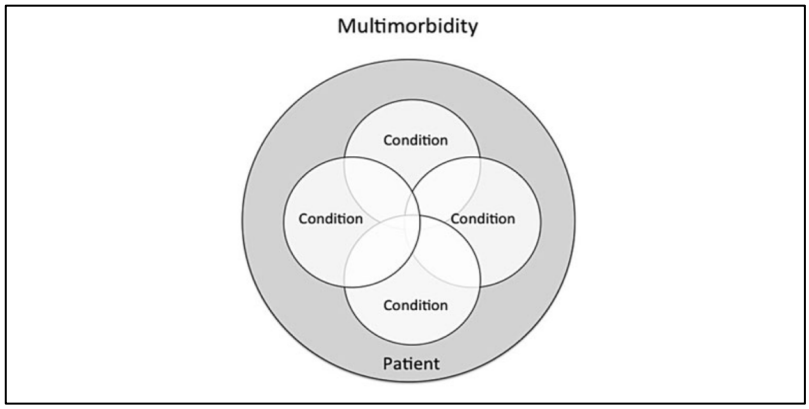
Figure 1: Conceptual diagram of comorbidity: Index disease with other comorbid diseases affecting its presentation and treatment.



Source: Boyd and Fortin, 2010, pp: 453

Conversely, multimorbidity signifies the simultaneous occurrence of two or more chronic afflictions, wherein no single disease assumes a pre-eminent role over the other diseases (Boyd and Fortin, 2010). The multimorbidity approach, as depicted in *Figure 2*, suggests that the underlying pathophysiology of various conditions may exhibit varying degrees of interaction and overlap, and may therefore require integrated strategies for effective therapeutic management (Boyd and Fortin, 2010).

Figure 2: Conceptual diagram of multi-morbidity: Multiple conditions unfolding within an individual's preferences and circumstances.



Source: Boyd and Fortin, 2010, pp: 454

Considering the differences between comorbidity and multimorbidity, it is clear that the provision of care for individuals using the latter approach requires more complex and integrated strategies (Skou et al., 2022). The overlap between clinical conditions and the unique context of a person's life warrants synergistic management, wherein the condition as well as the broader context in which these co-occurring diseases unfold are addressed (Boyd and Fortin, 2010). While patient-centredness is a fundamental principle in multimorbidity healthcare, current clinical approaches often focus on

individual diseases and neglect the intricate interplay between patients, diseases, the context, and the healthcare system (Sturmberg et al., 2017). This complicates optimal healthcare, clinical decision-making, and effective policy development in multimorbidity management (Sturmberg et al., 2017).

In summary, a multimorbidity approach encompassing a broader perspective of multiple conditions unfolding in context is necessary to consider the effects of biological, psychological, social, educational, cultural, economic, and environmental factors on the health outcomes of people living with multimorbidity (Skou et al., 2022). This perspective is crucial, given that the contexts in which diseases co-occur differ, which may require unique clinical management and policy development.

6.2. Prevalence of co-occurring diseases

The prevalence and profiles of co-occurring diseases vary between HICs and LMICs. A meta-analysis of community-based studies conducted in HICs and LMICs revealed an overall pooled prevalence of multimorbidity of 33.1% (Nguyen et al., 2019). However, the prevalence estimates were significantly higher in HICs (37.9%) compared to LMICs (29.7%) (Nguyen et al., 2019). In HICs, studies have reported prevalence estimates ranging between 35% and 45.7% in different regions, with an overall global prevalence of multimorbidity estimated as 37.2% (Chowdhury et al., 2023). Similar research conducted in LMICs indicates an estimated mean multimorbidity prevalence ranging between 7.8% to 21.9% (Arokiasamy et al., 2015, Afshar et al., 2015). Multimorbidity prevalence estimates vary between different countries, from 53.8% in Bangladesh, 65.6% among China's elderly population, to 60% in rural India (Gummidi et al., 2023, Zhang et al., 2022a, Khanam et al., 2011).

In South Africa, multimorbidity prevalence estimates range between 4% and 22% (Brady et al., 2022, Arokiasamy et al., 2015, Alaba and Chola, 2013). A systematic review found that multimorbidity ranged from low to moderate (3–23%) when studies included younger age groups and moderate to high (30–87%) when studies included more narrow age groups (e.g., 40 years and older) (Roomaney et al., 2021). While multimorbidity is a significant contributor to, and consequence of inequality in South Africa, it has been largely overlooked in research and there has been a lack of standardisation of studies which report multimorbidity estimates (Roomaney et al., 2023). Similar to many other LMICs, the South African health system faces multiple challenges to deal with multimorbidity, including inequities in healthcare availability and utilisation, fragmented and poorly capacitated healthcare systems, and poorly maintained information systems (Basto-Abreu et al., 2022). The strain on the health system imposed by multimorbidity is exacerbated when population multimorbidity profiles include co-occurring mental and physical health conditions (Daré et al., 2019), as is delved into in the following section.

7. Co-occurring physical conditions and mental health disorders

The research presented up to this point highlights the burden of co-occurring diseases and multimorbidity globally and in South Africa. The co-occurrence of chronic mental and physical health conditions is a particular global health challenge in both developed and developing countries (Daré et al., 2019). The co-occurrence of mental and physical health conditions significantly impacts individuals' health outcomes and is associated with suboptimal treatment adherence, lower quality of life, poor socioeconomic status and living conditions, and limited individual coping abilities (Daré et al., 2019, Sorsdahl et al., 2018, Arokiasamy et al., 2015). Comorbid mental disorders are also associated with higher rates of health care utilisation (Gijsen et al., 2001), with evidence showing that coexisting mental health conditions can lead to a 45% raise in healthcare costs per person living with a chronic physical illness (Naylor et al., 2012). The following section provides a theoretical review of the mechanisms by which mental and physical health conditions co-occur. This is followed by an empirical review of data demonstrating the burden of co-occurring mental and physical diseases and further substantiate research into this topic area in LMICs and in South Africa. The final section demonstrates how the determinants and outcomes of certain co-occurring physical and mental health conditions – specifically, depression, HIV, and diabetes – are unique to the South African context.

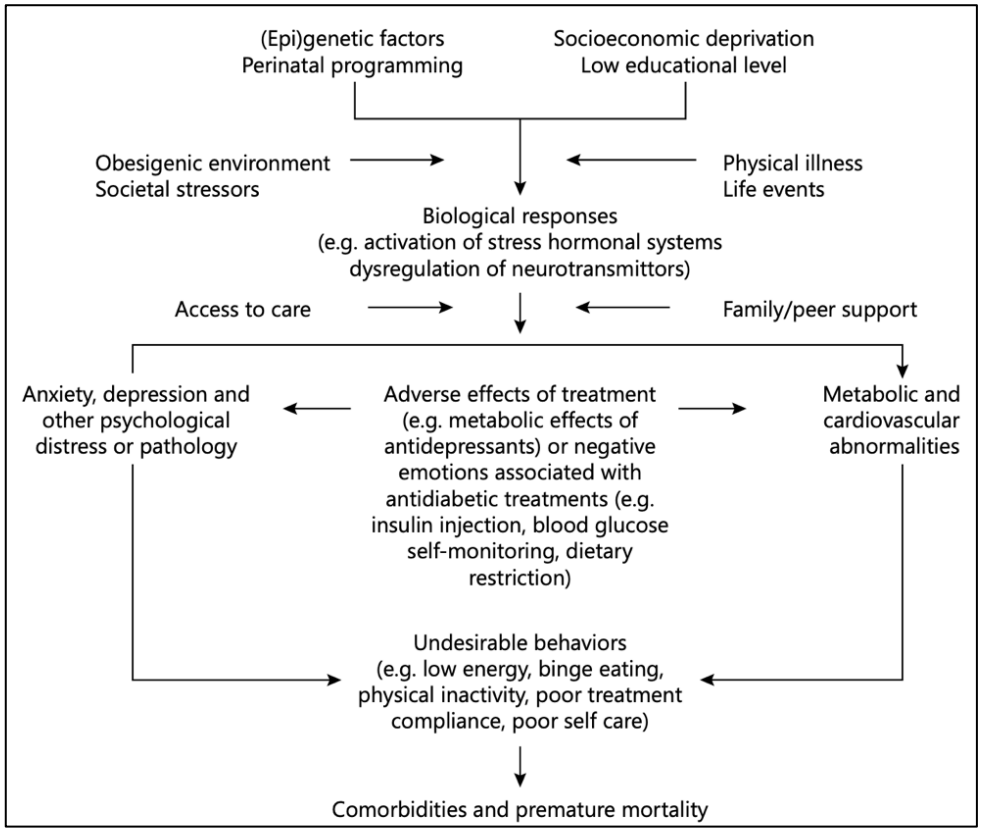
7.1. Theoretical review

Research indicates that individuals with mental disorders are at a higher risk of developing chronic physical diseases (Daré et al., 2019, Arokiasamy et al., 2015, Stubbs et al., 2015, Yu et al., 2015). Depression is associated with behaviours that increase the risk of non-communicable diseases (NCDs), such as a poor diet, substance abuse, smoking, and reduced physical exercise (Pryor et al., 2017). There are also other underlying mechanisms of chronic disease (for example, abnormalities of the biological stress response mechanisms) which may explain the link between depression with physical health (Pryor et al., 2017). Factors such as poverty, social isolation, poor access to nutrition, unemployment, and housing circumstances also contribute to individuals with mental health disorders being more vulnerable to develop chronic physical conditions (Canadian Mental Health Association, 2008). Conversely, individuals with chronic physical diseases are more likely to develop psychological conditions. In the context of diabetes, for example, high blood sugar levels have been shown to impact brain function, emotional stress, chronic pain, social isolation, and physical disability, which contribute to the development of psychological symptoms in individuals with diabetes (Canadian Mental Health Association, 2008). Depression prevalence among patients with chronic diseases like cancer, renal disease, heart disease, and COPD ranges between 13% and 79% (Daré et al., 2019; Solano et al., 2006). The risk for anxiety and/or depression in people with chronic physical diseases is increased by 310%,

Which poses significant intricacies to effective integrated mental and physical health interventions on an individual and policy level (Daré et al., 2019).

The relationship between physical and psychological disorders is underscored by shared underlying factors, including biological, psychological, socioeconomic, and cultural determinants (Sartorius et al., 2015). Various models have been developed to illustrate the interplay between these factors. *Figure 3*, developed by Sartorius et al. (2015), demonstrates how epigenetic factors, low socioeconomic status, and stressful life events can trigger hormonal interactions, leading to metabolic and cardiovascular disorders, creating a cycle of psychological and physical ill health (Sartorius et al., 2015). Social and economic contexts, including family, relationships, and broader societal elements, are also suggested to significantly influence mental and physical disorders in this model (Sartorius et al., 2015).

Figure 3: A model of mental and physical health disorder co-occurrence



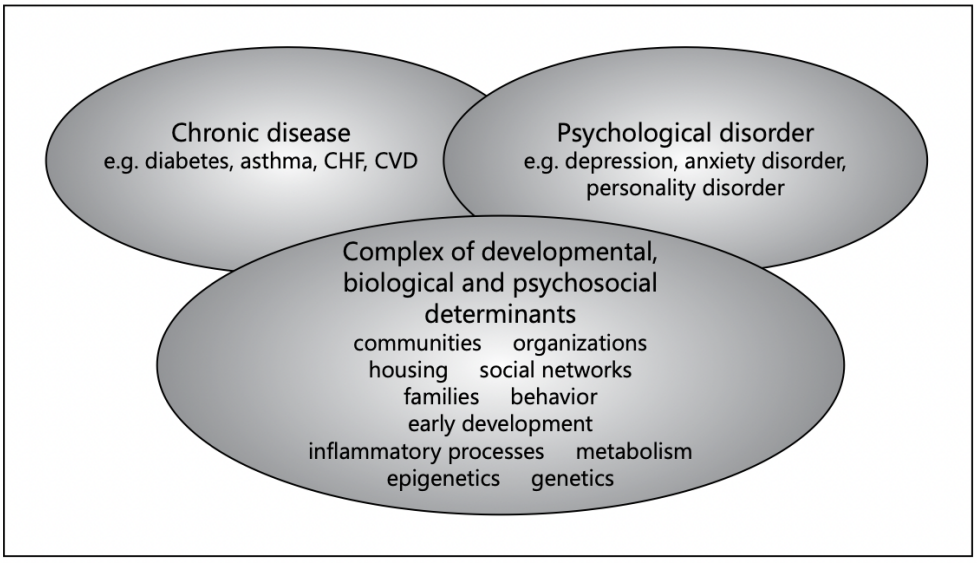
Source: Sartorius et al., 2015, pp:2

Although *Figure 3* suggests the interweaving of multiple levels of factors that lead to co-occurring physical and mental health conditions, it also suggests a unidirectional relationship between health or illness and the context in which it unfolds. This model neglects the effects of illness on a person's subsequent socioeconomic stratification, living conditions, access to healthcare, and experience of

social cohesion which means that the contextual and personal moderators and the consequences of the illness experience may be underestimated when using this approach.

Instead, it is widely recognised that the co-occurrence of mental and physical illnesses is influenced by various factors, largely influencing and influenced by the individual and household socioeconomic conditions and the context in which the disease co-occurrence unfolds (Pryor et al., 2017, Canadian Mental Health Association, 2008). A less complex illustration of the co-occurrence of mental and physical illnesses in *Figure 4* moves beyond the interaction between specific mental and physical health conditions due to pathophysiological or contextual pathways. Rather, this model considers health conditions as unfolding in a biosocial complex of events that make expression of physical and psychological multimorbidity more likely, and which reinforces or alters the determinants of illness (Sartorius et al., 2015). Thus, the expression of co-occurring physical and mental conditions differs depending on the context, while simultaneously shaping the context of those living with physical and mental multimorbidity.

Figure 4: Physical and mental illnesses as a biosocial complex of influences



Source: Sartorius et al., 2015, pp:7

While further development of the model in *Figure 4* is required to clarify the complexity of the relationships between the health outcomes (i.e., the diagnosis of chronic physical diseases and/or psychological disorders) and the various determinants of illness (i.e., developmental, biological, and psychosocial determinants), it highlights that the fundamental consideration of disease co-occurrence

should be its contextually dependent nature, rather than merely the order of disease diagnoses. This necessitates a comprehensive understanding of the relationships between physical and mental conditions within the broader environmental and social contexts for effective interventions.

7.2. Prevalence of co-occurring physical conditions and mental health disorders

The co-occurrence of physical and mental health conditions has received increased attention in research globally. Studies have shown statistically significant associations between mental health disorders and the diagnosis of chronic physical conditions, particularly in more deprived groups (Scott et al., 2016, Barnett et al., 2012). The pooled prevalence of anxiety and/or depression in people with chronic diseases is 36.6%, while the prevalence of diabetes and/or obesity in individuals with mental disorders is 16.2% (Daré et al., 2019). People with schizophrenia have a higher prevalence of diabetes (4 to 5 times higher) and individuals with bipolar disorders have a higher prevalence of diabetes (three times higher) compared to the general population (De Hert et al., 2006, McIntyre et al., 2005). In LMICs, where high prevalence of health risk factors and multiple chronic non-communicable diseases exist, the effects of co-occurring diseases are amplified, worsening health outcomes for affected populations (Thienemann et al., 2019). Despite the substantial burden of co-occurring mental and physical health conditions in LMICs, only a small portion (5%) of research originates from these countries, highlighting the need for better understanding of co-occurring diseases in diverse contexts (Thienemann et al., 2019, Xu et al., 2023).

In South Africa, coexisting mental-physical conditions present a threat to the sustainability of an already overburden and fragile health system (Petersen et al., 2019b). The prevalence of depression among patients with physical multimorbidities has been shown to increase as the number of physical diseases increases (Petersen et al., 2019b). This is a particular concern in South Africa, given the rising prevalence of physical multimorbidity, including the growing intersection between the epidemics of HIV and NCDs, and the growing effects hereof on the mental health of the population (Petersen et al., 2019a). While the South African Department of Health has recognised the problem of mental-physical multimorbidity and has introduced an integrated approach to management at the PHC level (namely, Integrated Clinical Services Management) (Mahomed et al., 2014), mental-physical multimorbidity remains an underserviced area of the South African health landscape, as demonstrated in the following section.

7.3. Empirical review

When considering the limited fiscal space in South Africa, as well as the devastating treatment gap for mental health conditions (Daré et al., 2019), it is clear that targeted interventions are required to

identify the most vulnerable population groups and combat specific mental-physical health condition clusters that contribute significantly to morbidity and mortality in South Africa (Petersen et al., 2019a). This section describes frequently co-occurring physical and psychological conditions in South Africa, particularly the co-occurrence of diabetes, HIV, and depression. While this scope limits the inclusion of other large contributors to the mental-physical multimorbidity burden in South Africa, such as hypertension, it is focused on these particular disease clusters to illustrate the confluence of a non-communicable disease, a communicable disease, and a mental health condition as it unfolds in the South African context.

7.3.1. Co-occurrence of diabetes and depression

The co-occurrence of diabetes and depression has been the topic of inquiry in a multitude of previous studies. A meta-analysis of studies in high-income countries indicates that individuals with depression have a 41% increased risk of type 1 diabetes and a 32% increased risk of type 2 diabetes (Yu et al., 2015). The underlying mechanisms of this relationship between depression and diabetes are not yet fully understood and require further research (Yu et al., 2015). Possible biological explanations include altered neurotransmitter activity, heightened inflammation, central adiposity, stress-related factors, and abnormalities in the hypothalamic-pituitary-adrenal axis commonly observed in depressed patients (Harris, 2003, Duncan et al., 2003, Björntorp, 1991). Behavioural factors such as poor diet, physical inactivity, and substance abuse are also common in both depressed individuals and those with chronic physical diseases, potentially contributing to this relationship (Knol et al., 2007). Beyond physiological and behavioural factors, it is essential to consider the broader social context driving the co-occurrence of depression and diabetes. For example, economic factors play a significant role in amplifying the bidirectional relationship between diabetes and depression in both high-income and low- and middle-income countries (Bukhman et al., 2015, Agardh et al., 2011). Researchers are increasingly exploring how the intersectionality of personal identities and socioeconomic conditions shape the co-occurrence of these health conditions, although further research is needed to the understand its complexity (Roomaney et al., 2021).

In South Africa, the influence of socioeconomic factors on the experiences of individuals with diabetes and depression have been studied (Mendenhall and Norris, 2015, Lund et al., 2010). The convergence of diabetes and depression in the country is concerning because of the ways in which poverty and depression can complicate the health problems related to diabetes (Lund et al., 2010). For instance, women in Soweto who have diabetes often experience psychological distress, which worsens as the number of co-occurring physical conditions increases (Mendenhall and Norris, 2015). Consequently, the combination of psychological stress from living with diabetes and their social circumstances affect

their dietary choices and diabetes management, leading to worsened health outcomes and further stress about their health and their capabilities to provide for their families in the future (Mendenhall and Norris, 2015). These findings emphasise the need for comprehensive investigations into the social dimensions of stress underlying diabetes and co-morbid depression in the South African context, especially since these experiences reflect the historically embedded systems of inequality and racism of the country. Furthermore, this highlights that understanding the co-occurrence of diabetes and depression requires a contextual lens to consider the socioeconomic factors (beyond physiological and behavioural mechanisms) that underscore the relationship between these conditions.

7.3.2. Co-occurrence of HIV and depression

The chronicity of HIV and the increasing lifespan of people living with HIV that has accompanied improved medical management and prevention strategies have led to increased research inquiries into the co-occurrence of HIV with other physical conditions and depression. The co-occurrence of depression and HIV has significant implications for the health of this population, including reduced adherence to ART, increased progression to acquired immunodeficiency syndrome (AIDS), worsened physical symptoms, higher mortality rates, and elevated risk behaviours contributing to HIV transmission, such as substance abuse and unsafe sexual practices (van Coppenhagen and Duvenage, 2019, Breuer et al., 2011, Ciesla and Roberts, 2001). There is strong evidence of a higher prevalence of depression among individuals living with HIV compared to the general population, with some studies finding nearly a twofold increased likelihood of depression (Qubekile et al., 2022, Breuer et al., 2011, Ciesla and Roberts, 2001). In LMICs, the relationship between depressive symptoms and HIV is associated with various other psychosocial and contextual factors, including poor social support, limited education, stigma, and economic hardship (Qubekile et al., 2022).

Multiple studies in South Africa have examined the association between depressive symptoms and HIV status or treatment. A geospatial analysis revealed that higher community HIV prevalence corresponds to increased individual risk of depression, although this occurrence varied significantly between provinces (Asare et al., 2022). In a study in Gauteng province, the prevalence of depression among people attending an ARV clinic was estimated at 53.8%, and lower CD4 counts were associated with more severe depressive symptoms (van Coppenhagen and Duvenage, 2019). While there are factors that reduce depressive symptoms among individuals people living with HIV, such as knowledge of HIV status, longer ARV use, and social support structures (Pappin et al., 2012), this co-occurrence of conditions is associated with slower rates of ART initiation, poor adherence, and worsened health outcomes (Truong et al., 2021). Contextual factors, such as poverty and the experiences of discrimination and internalised stigma among HIV-positive individuals at healthcare delivery points,

has been shown to especially worsen cognitive-affective depression (Simbayi et al., 2007). However, because these contextual factors vary significantly between provinces and healthcare sites (Asare et al., 2022, Simbayi et al., 2007), further research is warranted to illuminate the most crucial leverage points for effective context-specific interventions.

7.3.3. Co-occurrence of HIV, diabetes, and depression

While the associations of depression with HIV and diabetes have been studied respectively, limited research is available on the overlapping occurrence of these three health conditions. Previous studies have established the link between HIV, antiretroviral use, and an increased risk of diabetes, however the directionality of this relationship among many other personal and contextual factors remains unclear (Bosire, 2021, Oni and Unwin, 2015). Individual factors such as diet and body mass index are often mentioned as mediators in the HIV-diabetes relationship, globalisation, urban migration, and lifestyle changes in South Africa have also been linked with the co-occurrence of these chronic physical conditions and psychological symptoms (Bam et al., 2022).

A study conducted in Kwazulu-Natal province of South Africa found that a significant proportion of individuals with HIV and diabetes had symptoms of depression, but these were largely undiagnosed (Qubekile et al., 2022). The co-occurrence of HIV and diabetes was not directly associated with moderate to severe depressive scores, but these scores were linked to factors such as education level, quality of life, and gender among diabetic participants (Qubekile et al., 2022). The authors suggest that focusing solely on disease-related factors may overlook important social risk factors, particularly socioeconomic status, which could be the primary driver of depressive symptoms in this subpopulation (Qubekile et al., 2022). Studies of syndemic suffering in South Africa have also explored the clustering of non-communicable diseases, infectious diseases, and depression, to highlight the intricate interplay of social, psychological, and biological factors in shaping global health problems and people's experiences of disease within specific contexts (Mendenhall and Norris, 2015, Mendenhall et al., 2017, Mendenhall et al., 2022). For example, it was found that women living in poverty with HIV and diabetes perceive these overlapping social and health problems as mutually exacerbating, with priority given to their social challenges over medical issues (Mendenhall and Norris, 2015). The authors highlight the impact of structural violence, the HIV epidemic, and the legacy of apartheid on the experiences of depression among the women living in poverty (Mendenhall and Norris, 2015). Thus, social and medical problems interplay in specific populations and geopolitical contexts, which require social interventions beyond merely treating illness (Mendenhall et al., 2022). To inform such interventions, ongoing research is recommended to fully grapple with the contextual nature of the co-occurrence of these health conditions in various regions in South Africa.

8. Determinants of health

The literature discussed up to this point highlights the geographical variation in the prevalence of co-occurring health conditions, including population and socioeconomic variations between different countries and regions within countries (Nguyen et al., 2019, Thienemann et al., 2019, Oni and Unwin, 2015). The evidence supports ongoing research into the determinants of co-occurring diseases in context, including unpacking the population-specific demographic, socioeconomic, and cultural factors, as well as lifestyle, material and social factors in households, and factors related to the health system that contribute to these differences in order to respond adequately to the specific needs of different population groups (Afshar et al., 2015). This section focuses on the determinants of co-occurring health conditions by, firstly, unpacking the Commission on Social Determinants of Health (CSDH) framework as a conceptual basis for understanding how social determinants impact on health. This section then provides an overview of previous research conducted on the social determinants of co-occurring diseases, focusing on South African research.

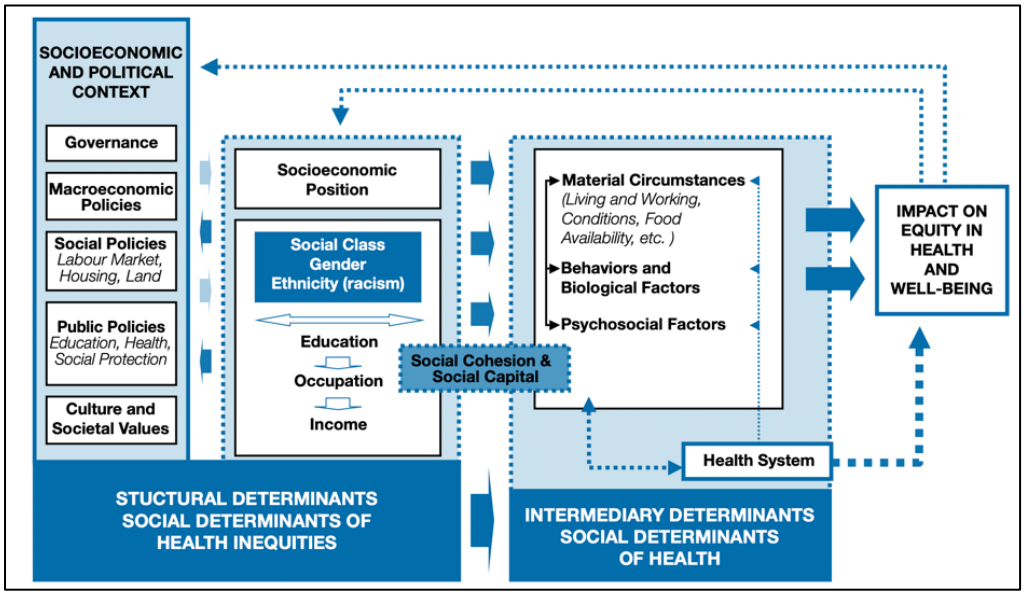
8.1. Commission on Social Determinants of Health (CSDH) framework

The CSDH framework appreciates that social, economic, and political mechanisms influence population groups differently, and that these factors stratify groups according to income, education, occupation, social class, gender, and ethnicity (Solar and Irwin, 2010). This socioeconomic stratification and the social status of groups shape the determinants of their health and vulnerability to illness (Solar and Irwin, 2010). The model, illustrated in *Figure 5*, posits that there are multiple other factors outside of personal genetics that affect the occurrence and severity of diseases, including environmental, behavioural, lifestyle, and socioeconomic factors (Solar and Irwin, 2010). The differential experience of illness and disability between groups perpetuates their social positions, perpetuating their economic and social hardships (Solar and Irwin, 2010). The CSDH framework points to the importance of understanding health and illness as determined by social processes and consequences. This framework has been used in previous research on the social determinants of multimorbidity conducted in South Africa (Alaba and Chola, 2013), in India (Puri et al., 2021), and in Jamaica (Craig et al., 2021), as well as in research on managing the effects of inequality of socioeconomic status on multimorbidity management among older people (Nwadiugwu, 2021), and on the historical, social and political contexts, and power relations that shape health inequalities in South Africa (Ataguba and Alaba, 2012).

The CSDH framework classifies the determinants of health as structural and intermediary factors (Solar and Irwin, 2010). These determinants are crucial to understand for policies and research to address

both the social factors that influence the health of populations (i.e., the determinants of health) and the social processes that cause and maintain the unequal distribution of social factors between different groups occupying unequal societal positions (i.e., the determinants of the inequalities of health) (Solar and Irwin, 2010).

Figure 5: CSDH conceptual framework



Source: Solar and Irwin, 2010, pp:6

8.1.1. Structural determinants

The CSDH framework posits structural determinants are factors that generate or reinforce social stratification in the society through its interplay between the larger socio-political context and individuals' and groups' socioeconomic positions (Solar and Irwin, 2010). These determinants maintain the social mechanisms and societal hierarchies that stratify health outcomes between various groups, therefore acting as the root cause of health inequities (Solar and Irwin, 2010). The main structural determinants include gender, ethnicity and social class.

Gender and ethnicity

Gender differences exist in the prevalence of co-occurring diseases. A systematic review found a greater prevalence of multimorbidity among women compared to men (Violan et al., 2014). Studies in South Africa show a higher prevalence of depressive symptomatology in females living with HIV (van Coppenhagen and Duvenage, 2019), of depressive symptomatology among women living with HIV and diabetes (Qubekile et al., 2022), of co-occurring NCDs in migrant and non-migrant females compared to males (Chukwuedozie et al., 2021), and of multimorbidity in females compared to males

(Brady et al., 2022, Alaba and Chola, 2013). Racial group differences have also been found in various studies on co-occurring diseases (Kronzer et al., 2023, Quiñones et al., 2019, Verest et al., 2019), Ethnic minorities have higher prevalence and earlier onset of multimorbidity (Verest et al., 2019). In South Africa, Indian/Asian and Coloured/Asian/Indian ethnicity associated with a higher prevalence of co-occurring diseases (Brady et al., 2022, Roomaney et al., 2021).

These differences between groups may be related to biological, socioeconomic, environmental, or cultural factors which affect the health of women and men differently across different ethnic groups (Weimann et al., 2016, Verdonk and Klinge, 2012, Vlassoff, 2007). Gender-related differences may be attributed to the social roles, stress and depression levels, and lifestyle habits that differ between gender groups, rather than to the biological differences between males and females (Chukwuedozie et al., 2021, van Coppenhagen and Duvenage, 2019, Alimohammadian et al., 2017). The historical differences in employment and educational opportunities between different racial groups, especially in South Africa, may also underscore the differences in disease co-occurrence between ethnic groups rather than biological differences (Weimann et al., 2016). Thus, the influence of race and gender on co-occurring diseases should not be analysed in isolation, and these differences in health profiles should be interpreted with caution.

Social class

According to the CSDH framework, social class is defined by the "relations of ownership or control over productive resources (i.e., physical, financial and organisational)" (Solar and Irwin, 2010, pp.28). Researchers often use educational attainment or income as a proxy to define social class (Craig et al., 2021). For example, in a study of the Hertfordshire birth cohort, Humphreys et al. (2018) found an association between paternal social class (as defined by paternal income) and increased multimorbidity when the child reached an age 64 to 68 years. Using the longitudinal study data from the Aberdeen Children of the 1950s (ACONF) cohort, an association between a lower social class at birth (classified according to paternal occupation) and a higher likelihood of self-reported multimorbidity in middle age has been found, with educational attainment partially mediating this relationship (Johnston et al., 2019). These studies draw important links between accumulative effects of adverse childhood circumstances and social class over the life course on multimorbidity in later life, including the effects of poor household income, chronic stress, and poor familial cohesion on children and adults' health (Johnston et al., 2019). However, these studies confirm the approach of the CSDH framework to use socio-economic position as an aggregate concept of socio-economic position in research to include both the material/economic base of social class (including the possession and

control of resources), as well as the prestige related to social class (including access to life chances based on socio-cultural factors) (Solar and Irwin, 2010).

Socio-economic position

According to the CSDH framework, socioeconomic position can be measured meaningfully at the three complementary individual, household, and neighbourhood levels (Solar and Irwin, 2010). Crucial factors that constitute socioeconomic position include occupational status, level of education and income level (Solar and Irwin, 2010). In a Brazilian multimorbidity study, the authors highlight how education and income inequalities differed across different regions in the country and respectively impacted health through different mechanisms throughout a person's life course (Bof de Andrade et al., 2022). While higher levels of income represent increased health-related disposable income and affordability of care, higher levels of education show the longer-term influences of childhood life circumstances on adult health (Bof de Andrade et al., 2022). Given this difference, research should investigate the effects of occupational status, level of education and income level on health respectively (Solar and Irwin, 2010).

Education

A higher prevalence of co-occurring diseases has been linked to groups with lower educational levels (Afshar et al., 2015, Arokiasamy et al., 2015, Khanam et al., 2011). A significant effect of individual and parental education level has been found on multimorbidity respectively, while the combination of lower individual and parental educational levels significantly increase the odds of having multimorbidity (Schramm et al., 2022). A systematic review and meta-analysis of multimorbidity research conducted in HICs and LMICs found that lower levels of education were associated with 64% increased odds of multimorbidity (Pathirana and Jackson, 2018). In South Africa, multimorbidity has been associated with having a lower level of education (Brady et al., 2022, Chukwuedozie et al., 2021, Roomaney et al., 2021). In KwaZulu-Natal province, Qubekile et al. (2022) found that depressive symptoms among people living with HIV and comorbid diabetes were significantly associated with lower education levels. Authors have questioned the directionality of the causal mechanism between multimorbidity, education, deprivation, and age, and recommended that research should continue to unpack these variables as they unfold in various contexts (Knies and Kumari, 2022).

Occupation

The temporal nature of the relationship between lower levels of household employment and multimorbidity cannot be explored using merely cross-sectional data, as this link may be mediated by various factors (Knies and Kumari, 2022). For example, the caring responsibility invoked by illness may move family members out of the labour market, or people with poor health may only be capable of

working certain jobs which can be found in deprived areas (Knies and Kumari, 2022). In fact, it may be the confluence between limited job availability and lack of quality public services in lower income areas that underscore the multimorbidity and patterns of unemployment (Knies and Kumari, 2022). In South Africa, multimorbidity has been linked to lower levels of household employment (Kamkuemah et al., 2022, Weimann et al., 2016) and unemployment (Alaba and Chola, 2013), while employment has been found to reduce the risk of co-existing mental health disorders among chronic disease patients (Petersen et al., 2019b). In contrast, Brady et al. (2022) found that multimorbidity was associated with being employed, with those unemployed having 36% lower odds of multimorbidity. The authors explain that the relationship between unemployment and poor health outcomes can be understood by unpacking the deprivation and social issues that arise from not having an income (Brady et al., 2022).

Income

The relationship between income and multimorbidity has not been consistently found across different contexts. In the systematic review by Roomaney et al. (2021), differences in income were not consistently associated with multimorbidity, with the relationship between wealth, employment, unemployment stress, and multimorbidity remaining unclear. In HICs, the odds of multimorbidity have been shown to be 4.4 times higher among participants with lower levels of household income (Ingram et al., 2021). While Knies and Kumari (2022) also discuss that income-related differences in multimorbidity may be related to age, earlier retirement, or reduced labour market attachment among people living with multimorbidity, the authors warn against interpreting relationships that are seemingly causal, without concurrently accounting for other factors of socioeconomic deprivation, such as education and employment. In the meta-analysis of Pathirana and Jackson (2018), increased risk for multimorbidity was found with decreasing income in four studies, except in the South African study conducted by Alaba and Chola (2013), wherein increasing income but lower education levels were associated with increased multimorbidity risk. The authors emphasise the importance of stratifying income-related results according to age and gender, as well as adjusting for demographic and social variables which may influence this relationship (Pathirana and Jackson, 2018).

8.1.2. Intermediary determinants

According to the CSDH framework, the intermediary or downstream determinants flow from the underlying structural factors that determine social stratification, to shape the differences in vulnerability to illness and health outcomes between groups and individuals (Solar and Irwin, 2010). Intermediary determinants include material circumstances, behavioural and biological factors, psychosocial factors, and health system factors (Solar and Irwin, 2010).

Material circumstances

Household living conditions, food insecurity, and geographical area differences

Research has considered the effects of the household living conditions on the co-occurrence of diseases. Larger family sizes have been linked to increased prevalence of co-occurring diseases in South Africa, with a suggested link between overcrowding, inadequate nutritional intake, and increased exposure to pollutants (Chukwuedozie et al., 2021). Ingram et al. (2021) found contradicting results, with homeownership and the social circumstances within households being associated with both an increased and decreased likelihood of multimorbidity depending on the context studied. Household food insecurity has been associated with greater odds for multimorbidity in older adults, although this is not consistent across settings (Smith et al., 2023). In South Africa, Petersen et al. (2019) found that household food insecurity is highly correlated with depression and alcohol misuse among patients with chronic physical diseases. Household food insecurity enlarges the risk of physical and mental illness multimorbidity, especially in the young and economically active population, and that these factors need to be considered to inform appropriate policy responses (Petersen et al., 2019b).

Both urban and rural area living have been found as risk factors for multimorbidity in South Africa (Roomaney et al., 2021). However, this risk seems to vary according to the province in which the household is situated, with a higher prevalence in rural households in KwaZulu-Natal or the Eastern Cape provinces (Roomaney et al., 2021). Asare et al. (2022) highlights KwaZulu-Natal, Gauteng, Mpumalanga, and Free State provinces as having the highest multimorbidity burden, especially where the depression hotspots overlap with the HIV hotspots in these provinces. Urban and coastal dwellers in South Africa also have higher odds of living with co-occurring diseases (Chukwuedozie et al., 2021). A study conducted by Weimann et al. (2016) reveal the spatial patterns of multimorbidity clearly reflect the historically bound socioeconomic disadvantage of geographical areas. This district-level analysis may have been unable capture the nuanced spatial differences in multimorbidity supporting further analyses to discern these differences at a smaller spatial scale, such as at the intra-provincial, urban-rural, or intra-urban spatial level, since these variations may be related to the differences in healthcare services available or the particular histories of certain areas (Weimann et al., 2016). Further research is required to highlight the most imminent determinants on the co-occurrence of chronic diseases on an intra-provincial level in South Africa (Basto-Abreu et al., 2022, Pati et al., 2020, Weimann et al., 2016, Lund et al., 2010).

Behavioural and biological factors

Age

Numerous studies show a higher prevalence of co-occurring diseases with increased age (Roomaney et al., 2021, Arokiasamy et al., 2015, Bähler et al., 2015, Barnett et al., 2012). However, younger populations in LMICs also experience a rise in multimorbidity due to increasing behavioural and environmental risk factors (Thienemann et al., 2019, Afshar et al., 2015, Alaba and Chola, 2013, Barnett et al., 2012). Importantly, the impact of age on multimorbidity varies with socioeconomic conditions (Barnett et al., 2012). Affluent areas have a 10- to-15-year delay in onset of multimorbidity compared to economically deprived areas, particularly in mental illness multimorbidity (Barnett et al., 2012). The relationship between multimorbidity, lower income-status and age should also be considered alongside biological factors and epidemiological differentials (Chang et al., 2019). For example, in South Africa, poorer and younger groups commonly have co-occurring HIV and anaemia as part of their multimorbidity profile, while richer and older groups predominantly have co-occurring cardiometabolic conditions (Chang et al., 2019). Older age groups also have higher odds of physical multimorbidity in South Africa, while younger groups experience more physical-mental health condition co-occurrence (Petersen et al., 2019b). Gender and age intersections also impact age-related multimorbidity. For example, in Khayelitsha, younger females are more likely to have co-occurring diabetes and hypertension and older men more likely have co-occurring hypertension and HIV, while these results can further be stratified according to ART usage (Oni and Unwin, 2015). Therefore, research interpretations of the relationship between age and multimorbidity should not occur in isolation from other factors to inform contextually appropriate interventions for people of different ages.

Obesity

There is a substantial body of research that supports the relationship between obesity and multimorbidity (Kivimäki et al., 2022, Zhang et al., 2022b, Mishra et al., 2021, Keetile et al., 2020, Jackson et al., 2015, Machado et al., 2013). The interconnectedness of obesity-related diseases accelerates the development of multimorbidity, with people living with obesity being at a five times higher risk of simple multimorbidity and 12 times higher risk of complex multimorbidity (Kivimäki et al., 2022). In South Africa, there is a strong positive association between chronic physical diseases, depression, and obesity (Alaba and Chola, 2013), with obesity found to be associated with co-occurring diseases and NCD risk factors (Roomaney et al., 2021, van Heerden et al., 2017, Shukla et al., 2014). Obesity has an established association with a higher likelihood of multimorbidity (Oni and Unwin, 2015), with a higher prevalence of depression among patients with diabetes (González-Castro et al., 2021), with a higher prevalence of multimorbidity among HIV-positive patients (Kim et al., 2012), and with a higher prevalence of diabetes among HIV-positive patients on ARTs (Dave et al., 2011).

Given the high prevalence of obesity in South Africa (approximately 49%) (Alaba and Chola, 2013), as well as the high prevalence of household food insecurity (70%), high prevalence of diabetes (37%), and insufficient weekly physical activity levels among young persons living with HIV in Cape Town (Kamkuemah et al., 2022), understanding obesity in the context of co-occurring depression among HIV and diabetes patients in the Western Cape province is crucial.

Substance abuse and treatment adherence

A significant body of research focuses on the mental-physical health condition co-occurrence and substance abuse. A study conducted in Switzerland revealed a higher prevalence of multimorbidity among HIV-positive individuals compared to HIV-negative individuals, with smoking having a strong impact on multimorbidity and cardiovascular risk (Hasse et al., 2015). Another study found that concurrent alcohol and tobacco use was associated with higher rates of chronic physical diseases, homelessness, substance use disorders, and use of mental health outpatient services (MacLean et al., 2018). In LMICs, alcohol consumption and smoking have been significantly associated with a higher prevalence of multimorbidity (Keetile et al., 2020, Alaba and Chola, 2013).

Considering the high coexistence of multimorbidity and substance use among adolescents and youth living with HIV in urban areas of The Western Cape province, understanding the relationship between substance use and co-occurring health conditions in the socioeconomic realities of the South African context is crucial for effective policy responses (Kamkuemah et al., 2022). Previous research has highlighted an association between alcohol use and multimorbidity with HIV or without HIV among older adults in rural northeast South Africa (Mpinganjira et al., 2023). In the Western Cape province, research has found significantly lower out-of-pocket (OOP) payments incurred by chronic physical disease patients with alcohol-use compared to those with depression (Mutyambizi-Mafunda et al., 2023). The authors suggest that this finding possibly relates to this group who, in favour of expenditure on alcoholic beverages, crowd out healthcare spending and display healthcare self-neglect (Mutyambizi-Mafunda et al., 2023). This is significant as effective treatments for alcohol use may reduce spending on alcoholic beverages while improving health outcomes for comorbidities such as HIV and diabetes.

Medication nonadherence among patients with co-occurring diseases is also a significant concern due to its impact on health outcomes and healthcare costs. In China, a study among older patients with multimorbidity and polypharmacy found a medication nonadherence rate of 31.8%, which was associated with factors such as sex, cognitive impairment, continuity of care with the same physicians, and high drug costs (Liu et al., 2023). In the United Arab Emirates, higher medication adherence has

been observed among older patients with multimorbidity, particularly those aged over 66 years, with higher incomes and health insurance coverage, while low adherence and increased out-of-pocket payment being associated with multimorbidity and socioeconomic factors, such as low income (Allaham et al., 2022). Another study conducted in the Western Cape province of South Africa revealed low levels of disease control among patients with chronic physical conditions and depression attending primary healthcare clinics (Folb et al., 2015). These studies emphasise the importance of understanding medication nonadherence in the context of co-occurring diseases, especially when patients face socioeconomic challenges.

Psychosocial factors

Relationship status, social stress, and social support

The role of relationships in the trajectory of health and multimorbidity has been examined in previous research. Wang et al. (2022) found that middle-aged adults who were not married had higher odds of experiencing multimorbidity, while those married for less than 10 years had higher odds compared to those married for 21-30 years after adjusting for lifestyle and socioeconomic factors. Social relationships have been shown to positively contribute to functional activity participation, reduced mortality, and lower risk of physical multimorbidity (Lawrence et al., 2019, Singer et al., 2019, Cantarero-Prieto et al., 2018, Olaya et al., 2017). Lower levels of social relationships and loneliness increase the risk of functional limitations for individuals with and without multimorbidity (Jiao et al., 2021, Singer et al., 2019). Happiness and social satisfaction generated through relationships are more important than relationship status alone in understanding co-occurring diseases, as unhappy marriages have been associated with equal or worse mortality risk compared to persons who have never been married, divorced, separated, or widowed (Xu et al., 2023, Lawrence et al., 2019).

Beyond relationship status, the influence of social support on multimorbidity has also been the focus of recent studies. Wicke et al. (2014) found that the relationship between social support and health-related quality of life is highly mediated by depressive mood, with depression having a greater influence than multimorbidity on patients' quality of life. A Canadian study showed that social support is strongly linked to lower odds of depressive symptoms among people living with multimorbid conditions, regardless of the severity of multimorbidity (Zhang et al., 2022b). Wang et al. (2023) discovered that community-level social support buffers the adverse effects of multimorbidity and frailty on psychological distress among older patients. These findings emphasise the importance of considering social factors in understanding and addressing multimorbidity.

In the South African context, associations have previously been found between multimorbidity and being married (Mukadas and Ushotanefe, 2021) and being separated, divorced, or widowed (Roomaney et al., 2021). Stress and mental health among individuals living with multiple chronic illnesses are highly intertwined with the social dynamics of people's everyday lives in South Africa. Social interactions with family and friends can provide support, but for some individuals, social circles contribute to stress, particularly in the context of poverty (Schmidt-Sane et al., 2023). Spiritual practices, faith, and societal acceptance have also been shown to assist individuals in South Africa in living with chronic illnesses (Bosire, 2021). Mendenhall et al. (2022) demonstrated how social stresses, including fear, family stress, financial hardship, and psychological comorbidity, interact and reinforce health conditions among individuals living with multimorbidity in South Africa. Thus, multimorbidity in South Africa is shaped by social realities and is not solely a medical diagnosis. Further research is needed to explore the role of social participation, isolation, and relationship satisfaction on the experience of people living with co-occurring diseases in the country (Mendenhall et al., 2022).

Self-efficacy

Self-efficacy is important in treatment adherence and disease management, especially when patients are living with multiple conditions. Research has shown that self-efficacy has a positive direct effect on diabetes education, self-management, and self-care practices, while reducing diabetes distress and depression (Devarajooh and Chinna, 2017, Kav et al., 2017, Nokes et al., 2012). Self-efficacy is a predictor of adherence to antiretroviral therapy (ART) among individuals living with HIV (Nokes et al., 2012), as well as increased disease control among patients living with HIV or diabetes (Devarajooh and Chinna, 2017). Self-judgement has also been identified as the strongest predictor of depressive symptoms among HIV positive individuals (Eller et al., 2014).

Research in Africa has primarily focused on self-efficacy in the context of HIV medication adherence and safe sex practices. Studies in Uganda and South Africa have found that self-efficacy plays a significant role in ART adherence, depression alleviation, and condom use among individuals living with HIV (Closson et al., 2018, Wagner et al., 2017). However, it is important to consider these individual-level psychosocial factors within the broader social and structural realities that influence the lives of people living with HIV (Closson et al., 2018). For example, research among men who have sex with men in Cape Town revealed a significant association between depression, lower self-efficacy, and unprotected sex, which in turn affected health outcomes (Tucker et al., 2013). These findings highlight why self-efficacy is important to study in the context of co-occurring health conditions.

8.1.2. Health system factors

According to the CSDH framework, the health system is an important, although often neglected intermediary determinant of health (Solar and Irwin, 2010). Health system factors directly correspond with the differences in exposure and vulnerability to illness as it affects equitable access to care, as well as intersectoral factors that affect the health status of different subpopulation groups (Solar and Irwin, 2010). Access has been defined by McIntyre et al. (2009) as "a multi-dimensional concept based on three dimensions: availability (or physical access), affordability (or financial access), and acceptability (or cultural access)" with "…the interaction between the dimensions that determines access" (pp:183-184). Accordingly, this section considers research available on access to the health system as a determinant of health as it relates to multimorbidity.

Availability

The availability of healthcare refers to whether appropriate services and providers are provided at the right time and place to meet the predominant needs of the groups it is intended to serve (McIntyre et al., 2009). Individuals with multimorbidity face challenges in accessing appropriate care, including long waiting times, difficulty accessing appointments at short notice, and inadequate appointment durations to discuss their multiple health issues (Millar et al., 2018). Factors such as poor health provider motivation, high workloads, and inadequate resources contribute to the limited availability of care for individuals with multiple conditions (Storla et al., 2008, Alberti et al., 2007). In LMICs, healthcare facilities often lack sufficient financing, effective screening and treatment options, and suffer from poor continuity and integration of disease management, resulting in polypharmacy and multiple visits to different providers (Basto-Abreu et al., 2022, Swinburn et al., 2019).

In South Africa, there are various barriers to healthcare access for people living with multiple conditions, including limited transportation, poor clinic services, insufficient ambulances for referrals, inconsistent drug supplies, and administrative challenges (An et al., 2022, Goudge et al., 2009). Travelling time and distance are major barriers to HIV testing and counselling, as well as the insufficient nursing knowledge, functional equipment, medicine shortage, and poor record-keeping limiting the management of NCDs, which results in higher rates of referrals to higher levels of care (Meehan et al., 2015, Musheke et al., 2013, Sekokotla et al., 2003). Understanding these unique factors affecting healthcare availability is crucial to improving access and reducing disparities in essential care for different groups in South Africa (Gordon et al., 2020).

Affordability

Affordability refers to the degree of fit between the individual or household's ability to pay and the full costs of accessing care among the other demands of the household budget (McIntyre et al., 2009). Affordability also relates to the impact of the costs of care and the use of household resources to fund healthcare on the household's wellbeing (McIntyre et al., 2009). Socio-economic disparities contribute to inequalities in healthcare utilisation, with individuals from financially advantaged backgrounds more likely to recognise their healthcare needs and seek care compared to those from lower-income areas who may postpone seeking care due to affordability constraints (Gordon et al., 2020). This pro-rich inequality in the perceived need for healthcare can delay access to care for individuals living with multiple conditions in lower income groups (McLaren et al., 2014, Harris, 2003).

In LMICs, there is a strong association between higher out-of-pocket expenditures and the number of outpatient visits and hospitalisations among patients with multiple co-existing NCDs (Lee et al., 2015). In South Africa, the incidence of catastrophic healthcare expenditure has been found to range from 5% to 66% (Cleary et al., 2013, Dyer et al., 2013, Goudge et al., 2009). This is partly due to significant indirect costs such as transportation expenses and the use of private providers without insurance, which limit the effectiveness of state-provided financial protection (Goudge et al., 2009).

The affordability of services for specific health conditions in South Africa varies. For instance, out-of-pocket expenses for diabetes healthcare create significant financial hardship for patients, with a 25% incidence of catastrophic health expenditure (Mutyambizi et al., 2019). While ARTs for HIV is provided free of charge in South Africa, there are substantial non-drug costs associated with accessing treatment that limit access, including transportation expenses, income losses, and the opportunity costs of participating in other activities (An et al., 2022, Pillai et al., 2019, Rosen et al., 2007). Studies have also estimated the direct and indirect costs associated with outpatient chronic mental illness care in the private sector, including medication costs and lost income due to illness (Lund et al., 2013). For individuals with severe depression or anxiety disorders, there is an estimated mean lost income of USD4,798 per adult per year, indicating the economic impact of mental illness in South Africa (Lund et al., 2013). When these conditions co-occur, both the direct and indirect costs of accessing healthcare intensifies which creates significant access barriers for patients and lead to delayed treatment (Bähler et al., 2015).

Acceptability

Acceptability is defined as the fit between patients and providers' attitudes and expectations (McIntyre et al., 2009). Research has previously identified patient expectations for care in the context

of multimorbidity, emphasising the need for tailored treatment, collaborative decision-making, and respectful relationships between patients and providers (Moody et al., 2022). Ultimately, care at a primary healthcare level should reflect patients' holistic needs and be built on trusting patient-provider relationships and open communication (Moody et al., 2022).

In South Africa, patient satisfaction with healthcare has been found to be generally high, but higher among patients from higher socioeconomic groups. Dissatisfaction with care is more prevalent among patients accessing public health facilities compared to private patients (Gordon et al., 2020, Myburgh et al., 2005, Harris, 2003). Dissatisfaction among patients accessing HIV care at PHC facilities in Cape Town is linked to access barriers like long waiting times, poor staff attitudes, HIV stigma, and inadequate privacy for counselling (Meehan et al., 2015). Additionally, a significant portion of participants with chronic illnesses could not accurately report their diagnoses, suggesting a breakdown in communication between patients and healthcare providers (Goudge et al., 2009). Understanding these dynamics is crucial for ensuring patients with co-occurring diseases have access to caring providers.

It is important to address access barriers without compromising the availability and quality of services for others or increasing the opportunity costs associated with care (Mabuto et al., 2019). The various aspects related to healthcare access interact in complex ways, influencing patients' decisions to seek care, their experiences in healthcare facilities, and the expectations of both patients and providers.

8.1.3. Strengths and limitations of the CSDH framework

The CSDH framework offers several strengths when applied to research on co-occurring disease, particularly in LMICs. Firstly, the framework is centered around the assumption that health is defined by complexity. The value of a framework that holds at its core that health is, in essence, a social phenomenon is that it allows a careful identification and inclusion of a large array of relevant determinants of health. By considering both structural and intermediary determinants of health, the framework offers a holistic perspective of the interconnectedness of factors that contribute to health outcomes and inequalities. The explicit focus on social determinants of health, including the influence of poverty, education, housing, and social support, enhances its relevance compared to traditional medical models, specifically in the ever-changing and unique contextual dynamics of South Africa where interventions that address these contextual factors are desperately required. The sound theoretical grounding and the inherently equity-oriented lens of the CSDH framework makes it useful when unpacking these complexities for effective policy making and action in real life settings (Krumeich & Meershoek, 2014). Thereby the findings of research become more relevant and

functional for policymakers aiming to prioritise interventions that address the root causes of health inequalities. Lastly, as the framework encourages an interdisciplinary and intersectoral approach to understanding and managing complex health system issues, it is highly relevant in research settings where there are dynamic and dynamically interacting pathways by which health is affected (Krumeich & Meershoek, 2014). This interdisciplinary approach can lead to innovative interventions that address the complex interplay of social, economic, and environmental factors that influence health outcomes when diseases co-occur.

However, while the sophisticated CSDH framework illustrates the complexities of health in context, it provides only general suggestions of potential elements and pathways. As a theoretical framework, it remains inherently abstract, offering a broad overview of potential factors and their interactions, and therefore, may lack the specificity to explain concrete interventions to improve health management in particular contexts (Krumeich & Meershoek, 2014). Whilst this general theoretical overview is often sufficient to guide research, it makes the framework impractical to address real life problems in specific settings (Krumeich & Meershoek, 2014). This is because the evolution of health pathways depends on historical processes and global relationships entangled in complex local dynamics which cannot fully be appreciated in a static model. As such, using the framework without explicitly considering local realities creates the risk of imposing global standards, innovations, or policies on local contexts where they may not be appropriate. Moreover, whilst the framework creates an awareness of the complex pathways underlying health disparities, enlisting these dynamics does not automatically assist in prioritising access points for policy interventions – be it at the structural or intermediary levels, or at multiple levels in the framework simultaneously. When research findings are organised within the parameters of the framework without stakeholder consultation or without consideration of the situatedness and uniqueness of particular local pathways, the development of sustainable and effective policies can be undermined (Krumeich & Meershoek, 2014). In the case of applying the CSDH framework in research on co-occurring disease, it is essential that statistics-based studies are supported by in-depth case studies or detailed, concrete analysis that takes the unique particularities of different settings into consideration. By supplementing the theoretical approach of the framework with contextual depth, the framework can be a useful guide to unpack the complexities underlying co-occurring diseases and the social determinants thereof.

In summary, while the CSDH framework offers a valuable theoretical perspective for understanding co-occurring diseases in LMICs, its practical application may be limited. To effectively utilize the framework, researchers should complement its theoretical insights with in-depth case studies and

careful consideration of local contexts. This approach can provide a more comprehensive understanding and inform the development of effective policies.

9. Methodological review

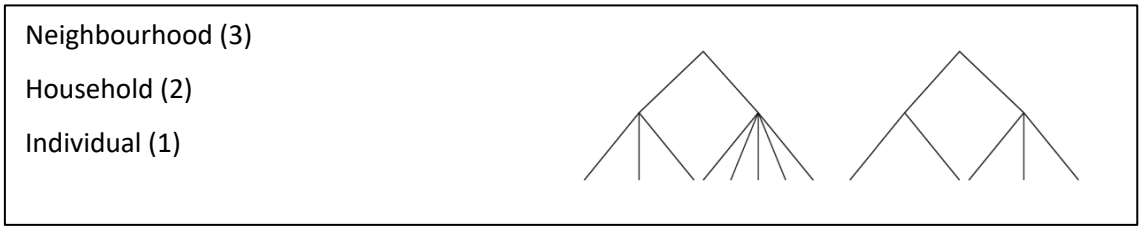
From the literature presented up to this point, it is clear that studying co-occurring disease necessitates an understanding of the context in which it occurs, as the determinants thereof are situated at both individual and contextual levels. This section offers an overview of the methodology supporting multi-level analysis in public health research. Previous public health research conducted with the use of multi-level analysis in South Africa is summarised to substantiate the use of this methodology in research on the socioeconomic determinants of depressive symptoms among patients living with HIV and/or diabetes.

9.1. Multi-level analysis methodology

9.1.1. What is a multi-level model?

Multi-level models are types of regression models that are used when the data has a hierarchical structure. Whilst a regression model (single level) estimates the mean or intercept, a multi-level model "summarises the distribution of the higher-level units for all contexts using the population mean and the variance" (Leyland and Groenewegen, 2020, pp: 34). Different individuals living in the same communities will have a common contextual factor that influences their health, which may not be shared by those from other neighbourhoods, while they might simultaneously have different factors that influence their health related to their individual health behaviours, household composition, or differing socioeconomic conditions (Leyland and Groenewegen, 2020). Multi-level analysis (MLA) can partition this variation into the fragment that is attributable to the individual and the fragment attributable to the neighbourhood. Samples of these different contexts can be collected, measured, and analysed, and are called *levels* in MLA (Leyland and Groenewegen, 2020). These levels or hierarchies are organised into a pyramid structure in MLA, with individuals or patients at the lower level (level one) where the outcome is measured, nested within their context at the higher levels (level two, three, and so forth), as depicted in *Figure 6*. This hierarchy allows for the possibility that the individual outcome may be influenced by the shared context with other individuals (such as factors relating to the same hospital attended by patients, or the same safe outdoor spaces individuals can access in the neighbourhood) (Leyland and Groenewegen, 2020).

Figure 6: Example of a basic three-level model



Source: Leyland and Groenewegen, 2020, pp:50

There are characteristics that vary between the different contextual levels (levels 2 and up), which is either directly related to the level units (such as neighbourhood crime level) or to an aggregate of individual characteristics (such as average socioeconomic status) (Leyland and Groenewegen, 2020). The variation at the higher level – for example, the neighbourhood – contains the variation of the outcome of each neighbourhood around the overall average (Gelman and Hill, 2006). MLA assumes that neighbourhood averages are drawn from a distribution of all neighbourhood averages, akin to a random effects analysis of variance (Gelman and Hill, 2006). Thus, the neighbourhood average can be conceptualised as a regression intercept. The term *random intercepts model* arises from the assumption that these macro-level intercepts are drawn from a statistical distribution encompassing all possible intercepts (Gelman and Hill, 2006).

In MLA, there is an assumption of a normal distribution for data at the higher-level units. This implies that the estimated effect for each individual unit is shrunk to the mean for all units, depending on the availability of information on the higher-level units and the extent of data clustering (Leyland and Groenewegen, 2020). Data clustering is summarised by an intraclass coefficient (ICC) which calculates the proportion of the total variance attributable to higher level units (Merlo et al., 2005). The ICC also summarises the correlation of the outcomes (ranging between no correlation – 0 – and perfect correlation – 1) between different lower-level units nested within the same higher-level unit (Merlo et al., 2005). Therefore, the effect estimated for each higher-level unit is a weighted average of unit-specific data and the population average. In the case where there is limited information about a specific higher-level unit, there would be limited evidence that the effect of the unit differs from the average, resulting in more significant shrinkage towards the mean (Leyland and Groenewegen, 2020). This process, known as "borrowing strength" (Ghosh et al., 1998), allows units with limited information to benefit from the information available in the collective sample. This introduces a level of uncertainty around the estimate, with larger confidence intervals reflecting lesser amounts of available information for the specific unit (Leyland and Groenewegen, 2020).

9.1.2. Multi-level analysis in public health research

The growing recognition of the significance of health in context amongst public health researchers has implied that research should reflect the principle that individuals' well-being is influenced by the contexts or environments in which they reside (Leyland and Groenewegen, 2020). Thus, when discussing or researching health, it should be inherent to address two distinct levels: the individuals and their contextual surroundings (Leyland and Groenewegen, 2020). MLA is a useful method in public health research that posits that the areas in which people live affect their health.

Multi-level analysis (MLA) is the most suitable statistical tool to effectively navigate the complexity of health as it operates at different levels of the context (Leyland and Groenewegen, 2020). When the correlation among individuals within their contexts is not considered or the clustering of individuals within higher contextual levels, this can result in an overestimation of the effective sample size, or *misestimated precision* (Aitkin et al., 1981). MLA is a method that can move beyond the assumptions of regression analysis that each individual's health outcomes are independent – an assumption that regards individuals as isolated from the macro contexts in which they operate. MLA is especially useful in research that examines the issues of health inequities, including research questions regarding varying health behaviours and outcomes, social determinants, and access to healthcare between groups. When health-related factors vary significantly between cities or geographical areas, between different neighbourhoods or communities, or between individuals with different socioeconomic circumstances or cultural backgrounds, MLA enables analyses to consider individual-level outcomes relating to the independent variables at the individual level, as well as the independent variables at the contextual or macro levels (Leyland and Groenewegen, 2020). Examples of contextual levels of influence that are relevant to public health research includes administrative areas (such as districts), healthcare service areas (such as clinics), social units (such as communities or neighbourhoods), or disease exposure areas (Leyland and Groenewegen, 2020).

9.1.3. Multi-level analysis in public health research in South Africa

Multi-level modelling assists in understanding the micro–macro relationships between individuals and their context, which is useful in LMICs where individual health is intricately linked to contextual factors (Leyland and Groenewegen, 2020). This is an essential approach to research in South Africa, where contextual factors, including socioeconomic and political conditions, are inextricably linked to individual and community health (Coovadia et al., 2009). Previous research has been conducted in South Africa using multi-level modelling, of which eight research papers have been reviewed to illustrate the relevance of this approach (summarised in Table 1).

The reviewed literature in which multi-level modelling was applied focused on various health conditions, including self-rated health (Lau and Ataguba, 2015), depressive symptoms (Dowdall et al., 2017; Tomita and Burns, 2013), tuberculosis (Dhlakama et al., 2022; Harling et al., 2008), abdominal obesity (Kamkuemah et al., 2023), risky sexual behaviours (Odimegwu and Ugwu, 2022), and missed vaccination opportunities (Uthman et al., 2018). Of the eight articles, six used a cross-sectional design and two used a longitudinal design. Five studies used nationally representative data from one or more of the waves of the South African National Income Dynamics Study (data collected between 2008 and 2017) (Dhlakama et al., 2022; Odimegwu and Ugwu, 2022; Dowdall et al., 2017; Lau and Ataguba, 2015; Tomita and Burns, 2013); two studies used data from the South African Demographic and Health Survey collected during 1998 and 2016 respectively (Odimegwu and Ugwu, 2022; Harling et al., 2008); one study used data from Demographic and Health Survey data collected between 2007 and 2016 across 35 Sub-Saharan African countries (Uthman et al., 2018); and one study used a small sample (N=87) of adolescents and youth living with HIV who attend primary healthcare facilities in peri-urban Cape Town (Kamkuemah et al., 2023).

It is notable that all the reviewed studies made use of a multi-level model, except for the paper by Dowdall et al. (2017). This analysis used cluster corrected standard errors and survey regressions although this approach did not include a multi-level model (Dowdall et al., 2017). Whilst this method was appropriate to identify that neighbourhood-level deprivation had an impact on depressive symptoms, the authors acknowledge that a multi-level model would have allowed for a more in-depth examination of the simultaneous impact of both individual- and group-level predictors on individual-level outcomes (Dowdall et al., 2017). Similarly, while Lau and Ataguba (2015) concluded that their analysis could have been conducted without the hierarchical structure of a multi-level model, since the variance remained the largest at the individual level, compared to household and neighbourhood levels, the authors note that the multi-level model remains the best approach to holistically consider the relationship between different predictors and health as it unfolds in various contexts.

Of the studies included in the review that made use of multi-level modelling, four studies included two level models – with the individual as level 1 (in all 4 studies) and the province (1 study) or neighbourhood (3 studies) as level 2 – and three studies included three level models. The three level models included the individual-level as level 1, households or neighbourhoods as level 2, and Magisterial Districts of residence, neighbourhoods, or country as level 3. Six of the studies, excluding the study by Lau and Ataguba (2015), found significant variation in the outcomes attributable to the levels 2 and/or 3 by measures of variation such as the Intra-class Correlation Coefficient (ICC) and

Proportional Change in Variance (PCV). Previous studies using this method in African demographic research have been criticised for the failure to interpret the measures of variation, as this undermines the purpose and goal of multi-level modelling (Odimegwu et al., 2023). A major strength of these seven studies reviewed was the acknowledgement that the multi-level modelling method differs from other methods which mainly focus on the fixed effects, and that the interpretation of results discussed both the fixed effects and random effects.

Overall, previous research conducted in South Africa using multi-level modelling supports the use of this method to appreciate the influence of the context on health and health behaviours. The available research highlights that different community-, neighbourhood-, province-, and country-level interventions may be required to effectively address these different contextual influences.

Table 1: South African research using multi-level modelling as a methodology

Author and title	Study period; Location	Sample	Study design	Study variables	Statistical methods	Findings from the study
A Multilevel Analysis of the Associated and Determining Factors of TB among Adults in South Africa: Results from National Income Dynamics Surveys 2008 to 2017 (Dhlakama et al., 2022)	2008 – 2017 South Africa	Nationally representative sample from the South African National Income Dynamics Study, including , Wave 1 (2008), Wave 2 (2010), Wave 3 (2012), Wave 4 (2014/2015) and Wave 5 (2017). Sample sizes of the waves (1-5) were respectively 7,102, 18,585, 21,313, 23,487, and 25,076.	Longitudinal data	The NIDS data has a hierarchical structure from repeated observations (waves) nested within individuals, which are nested within households, geographical types, district councils, and provinces. **Dependent variable:** Self-reported tuberculosis **Independent variables:** marital status, age, gender, race, education, home language literacy, employment status, smoking, suffer from other diseases (including physical, sight, hearing or speech, or psychological disorders, HIV/AIDS, Epilepsy, Emphysema and Alzheimer's disease), regular exercise, consultation with health practitioner, asthma, diabetes, social grant, household income, access to better housing, household expenditure, and geographical type.	The logistic regression model for the fixed effects factors selected by stepwise regression was used first. This was followed by a Generalised Linear Mixed Model, which included a two-level random intercept model with the fixed effects of the logistic regression model and province as a random effect. The two model levels included the province and individual-level. The models were applied to all 5 waves.	The frequentist and Bayesian models resulted in the same factors identified as associated with TB. The ICCs indicate that level two (province level) contributed 4.8%, 3.2%, 4.3%, 5.2%, and 6.2% to the variation in TB, for waves 1 to 5 respectively. Factors associated with TB consistently between wave 1 to wave 5 included age, suffering from other diseases, smoking, and consultation with a health practitioner. Other factors also identified as associated included marital status, gender, race, unemployment, regular exercise, diagnosis with asthma, diabetes, housing, household income, and geotype.

The association between neighbourhood-level deprivation and depression: evidence from the South African National Income Dynamics Study (Dowdall et al., 2017)	2007 - 2008 South Africa	Nationally representative data (N=11,955) from the first wave (2008) of the South African National Income Dynamics Study and the South African Indices of Multiple Deprivation (SAIMD). SAIMD include deprivation domains: income and material, employment, education, and living environment.	Cross-sectional	**Dependent variable:** Depressive symptoms **Independent variables:** 1) Area-level deprivation indicated by deprivation indices used in the SAIMD 2) Individual-level covariates: age, gender, marital status, employment status, education level, income, negative life events, durable goods, and individual-level living environment deprivation variable	Cluster corrected standard errors and survey regressions (not a multi-level model). Bivariate correlations were estimated between depression and neighbourhood-level variables. Models were controlled for individual-level covariates.	A significant positive association was found between depression and neighbourhood-level deprivation, with the most significant domains predicting this relationship identified as living environment deprivation and employment deprivation.
The social epidemiology of tuberculosis in South Africa: A multilevel analysis (Harling et al., 2008)	1996 – 1998 South Africa	Data from the 1998 South African Demographic and Health Survey (SADHS) and the 1996 South African national census. (N=3,826 respondents to the SADHS adult health questionnaire)	Cross-sectional	**Dependent variables:** Tuberculosis outcomes (consisting of (1) recent tuberculosis – diagnosed in the past year, (2) lifetime tuberculosis – diagnosed with TB ever) **Independent variables:** 1) Individual-level variables: age, race, education, employment, work in a mine / gold mine, urban residence, smoking, alcohol use, CAGE score, BMI.	Multivariate analysis was conducted with a three-level hierarchical model including fixed effects and group-level intercepts as random effects: individuals nested within households, and households nested within Magisterial Districts of residence. All multivariate models were adjusted	Tuberculosis diagnosis was associated with lower level of personal education, unemployment and lower household wealth, as well as cigarette smoking, alcohol consumption and BMI. The model including individual- and household-level factors found an increased prevalence of tuberculosis associated with high levels of community income inequality and lower household wealth quintiles, although being part of the wealthiest

				2) Household-level variables: number of adults per room, meals missed, and asset score quintile. 3) Community-level variables: Headcount poverty rate, Unemployment rate, Gini coefficient, and Robin Hood index	for clustering at the provincial level. Explanatory variables identified as significant in bivariate analysis were included in the model. Regression models were constructed to examine individual- and household-level variables for each outcome variable. Each community-level variable was subsequently added individually (given the high degree of correlation between these variables).	quintile was found to have a significant protective effect. The model including the community-level SES variables had minimal effect on the associations of the previous models. The model including community-level Gini coefficients identified that the associations found in the crude analysis remained significant. Participants living in districts with the greatest income inequality had more than double the odds of having tuberculosis.
Multilevel correlates of abdominal obesity in adolescents and youth living with HIV in peri-urban Cape Town, South Africa	2019 Cape Town, South Africa	Sample (N=87) from adolescents and youth living with HIV (AYLHIV) aged 15–24 years attending primary healthcare facilities in peri-urban Cape Town in 2019. Eight health sub-districts were sampled from,	Cross-sectional	**Dependent variable:** Abdominal obesity (waist-to-height ratio ≥ 0.5) **Independent variables:** 1) Neighbourhood-level: neighbourhood built and food environments 2) Community-level covariates: stigma, neighbourhood social capital, exposure to	The multi-level model structure consisted of participants (level 1) nested within neighbourhoods (level 2) with sub-districts used as a proxy. Variables associated with abdominal obesity in bivariate analysis and in	Multilevel models identified that skipping breakfast was associated with higher odds of obesity, while wholegrain consumption, physical activity, anticipated stigma, land-use mix diversity, access to recreational places, higher perceived pedestrian and traffic safety and having a non-fast-food restaurant within walking distance were associated with reduced odds of obesity. The ICC

(Kamkuemah et al., 2023)		namely Eastern, Western, Northern, Southern, Khayelitsha, Klipfontein, Tygerberg and Mitchells Plain		community violence and crime safety. 3) Household characteristics: thermal comfort in the home, food security, physical dwelling characteristics, family structure and orphanhood. 4) Individual-level covariates: (demographics) age, sex, educational attainment, socio-economic status, history of pregnancy and number of children, (clinical) anthropometrics, blood pressure and family medical history, knowledge and behaviours, and physical activity.	literature were included in the model. The relationships between the outcome (obesity) and factors associated with the different levels were estimates with bivariate logistic regression models and the multi-level logistic models adjusted for age and sex.	ranged between 0.01 and 0.2, showing some variability between and within sub-districts.
Investigating the relationship between self-rated health and social capital in South Africa: a multilevel panel data analysis	2008 – 2010 South Africa	Nationally representative sample from the South African National Income Dynamics Study, including, Wave 1 (2008) and Wave 2 (2010). Final sample used for analysis was N=8866	Longitudinal data	**Dependent variables:** individual self-rated health **Independent variables:** 1) Social capital variables: ● Individual-level: group participation, personalised trust and generalised trust. ● Household-level: reciprocity and associational activity. ● Neighbourhood-level was determined by aggregating the individual- and	A multi-level analysis was conducted to examine the association between social capital indicators and self-rated health, with individuals (L1) nested within households (L2), nested within neighbourhoods (L3) while controlling for relevant covariates on	The variance components between the null model and the subsequent models show minimal changes, with the variance remaining the largest at the individual level compared to the variance at the household and neighbourhood levels. The authors conclude that the analysis may therefore have be conducted without the hierarchical structure. Predictors that were identified as positively associated with self-rated

(Lau and Ataguba, 2015)				household-level social capital variables to the neighbourhood. 2) Covariates: ● Individual-level: self- rated health, obese, smoking, age, sex, race, marital status, education, employment status, urban, and number of household members. ● Household-level: household size and household income quintiles per capita. ● Neighbourhood-level: neighbourhood living environment deprivation index.	all three levels. Standardisation of self-rated health by age and sex was applied. Eight mixed-effects linear models were fitted: Model 0 as the null model; Model 1 including only covariates without social capital indicators; and Models 2 to 6 building on Model 1 by separately adding on each of the following variables: personalised trust, generalised trust, norms of reciprocity, norms of association, and various types of group memberships; and Model 7 as the full model with all variables.	health included personalised trust, individual community service group membership and neighbourhood personalised trust. Both individual- and contextual-level social capital factors were found to be associated with self-rated health.
A multilevel mixed effect analysis of neighbourhood and individual level determinants	2016 South Africa	Nationally representative sample (N= 3889; 1268 males and 2621 females aged 15-24 years), from the 2016 South Africa	Cross-sectional	**Dependent variables:** risky sexual behaviours (consisting of (1) multiple sexual partners and (2) unprotected sex)	A bivariate multi-level logistic regression was performed to determine the relationship between individual and neighbourhood-level	For multiple sexual partners: Model 1: 48% and 14% of variability (for females and males respectively) attributed to different neighbourhoods. Model 2: 6% and 21% of variation attributed to differences across

of risky sexual behaviour among young people in South Africa (Odimegwu and Ugwu, 2022)		Demographic and Health Survey.		**Independent variables:** 1) Individual-level factors: age, educational attainment, employment status, and household size. 2) Neighbourhood factors: urban or rural place of residence, Province of residence, community poverty, ethnic diversity, residential mobility/ instability, head of the household, community literacy level, and contraceptive media exposure.	factors. This was followed by a multivariate two-level mixed-effects logistic regression model, with youth (level 1) nested within neighbourhoods (level 2). Four models were sequentially fitted: Model 1 (empty model) tested random intercept variability and total variance in risky sexual behaviour across neighbourhoods; Model 2 examined individual-level determinants; Model 3 examined neighbourhood effects; and Model 4 examined the combined impact of individual and neighbourhood-level determinants.	neighbourhoods, with 24% and 47% of the variance explained by individual characteristics. Model 3: 8% and 10% of variability attributed to differences across neighbourhoods, with 86% and 29% of the variance explained by neighbourhood level characteristics. Model 4: 10% and 14% of variability attributed to differences between neighbourhoods, with 100% and 51% of the variations are explained by both individual and neighbourhood-level determinants. For unprotected sex: Model 1: 6% and 8% of variability (for females and males respectively) attributed to different neighbourhoods. Model 2: 5% and 10% of variation attributed to differences across neighbourhoods, with 24% and 36% of the variance explained by individual characteristics. Model 3: 16% and 28% of variability attributed to differences across neighbourhoods, with 76% and 79% of the variance explained by neighbourhood level characteristics. Model 4: 11% and 43% of variability attributed to differences between

						neighbourhoods, with 86% of the variations are explained by both individual and neighbourhood-level determinants. Youth from a heterogeneous ethnic groups or household size of more than five members, exposed to community education, were employed, and from high-level community poverty were associated with reduced odds of risky sexual behaviours. Older youths, those with secondary education attainment, from Gauteng province, with residential mobility, and with community media exposure to contraceptives were associated with increased odds of risky sexual behaviour.
A multilevel analysis of association between neighbourhood social capital and depression: Evidence from the first South African National Income	2008 South Africa	Nationally representative data (N=16,800 adults from 7300 households) from the first wave (2008) of the South African National Income Dynamics Study.	Cross-sectional	**Dependent variable:** Depressive symptoms **Independent variables:** 1) Neighbourhood-level social capital using data on association activity, support networks and reciprocity, safety, and collective norm and values. 2) Individual-level covariates: civic participation and social trust, as well as gender, race,	Multilevel models consisted of two levels – the individual and neighbourhood - estimated the association between individual depression outcome and neighbourhood social capital indicators. Four random intercept models were fitted sequentially.	A negative correlation was observed between depression scores and neighbourhood-level social capital, influenced by social trust and neighbourhood preference. Structural social capital, including civic participation, did not show a significant association with depression. Significant covariates of depression included individual factors such as social class, self-rated health status, and education.

Dynamics Study (Tomita and Burns, 2013)				marital status, employment, educational attainment, age group, social class, and current health status.		
Does it really matter where you live? A multilevel analysis of factors associated with missed opportunities for vaccination in sub-Saharan Africa (Uthman et al., 2018)	2007 – 2016 Sub-Saharan Africa	Demographic and Health Survey data collected between 2007 and 2016 in sub-Saharan Africa. We analysed data on 43,637 children aged 12 to 23 months (Level 1) nested within 15,122 neighbourhoods (Level 2) from 35 countries (Level 3).	Cross-sectional	**Dependent variables:** missed opportunity for vaccination. **Independent variables:** 1) Individual-level variables: child's age, sex, high birth order, number of children under five in household, maternal age, employment status, and education, media access, and wealth index. 2) Neighbourhood-level factors: neighbourhood socioeconomic disadvantage (quintiles). 3) Country level factors: human development index (country's intensity of deprivation; quintiles).	Multivariable multi-level logistic models (3 levels) analysed the association between missed opportunity for vaccination and individual and contextual factors, with the child (at L1), nested in a neighbourhood (at L2) living in a country (at L3). Five models were fitted. Model 1 was a model without any determinant variables. Model 2 included individual-level factors. Model 3 included neigh-bourhood-level factors. Model 4 included country-level factors. Model 5, included individual-, neighbourhood- and country-level factors.	Intra-country and intra-neighbourhood correlation coefficients indicated that 18.4% and 37.4% of the variance in the outcome could respectively be attributed to country- and neighbourhood-level factors. Significant risk factors for increased odds of missing vaccinations were found to include high birth order, high number of under-five children, poorest households, lack of media access, lack of maternal education and living in poorer neighbourhoods.

10. Conclusion

The review of the literature highlights that the global health burden is increasing and will continue to do so as the longevity of the population increases. Although communicable and non-communicable diseases, and mental health disorders create major burdens on health systems when these conditions occur respectively, the evidence presented highlights that it is the co-occurrence of these diseases that require the attention of researchers and policymakers globally. Specifically, a growing concern in LMICs is the high prevalence of co-occurring mental and physical health conditions. The evidence presented in this literature review on the prevalence and consequences of co-occurring HIV and diabetes with depression in South Africa illustrate this burden and highlight the importance of unpacking this phenomenon in context.

An important theme highlighted throughout the literature is that the social determinants of co-occurring diseases require research and policy attention. This is essential in South Africa with its quadruple disease burden and the perpetual cycles of socioeconomic disadvantage and entrenched divide between subpopulation groups that historically construct the inequitable distribution of co-occurring diseases between South African provinces. There are a multitude of factors, including individual, household, and health system factors that act as determinants of this disease co-occurrence, although these factors vary significantly between contexts and groups.

Further research is needed to investigate the socioeconomic determinants of depressive symptoms among persons living with HIV and/or diabetes in South Africa, as this topic remains important to inform effective policy interventions. While existing research has explored the influence of socioeconomic factors on individuals with diabetes, HIV, and depression in the Western Cape province, the convergence of diabetes and HIV with depression in South Africa raises questions about to what extent household- and community-level factors contribute to health problems and outcomes (Mendenhall and Norris, 2015, Lund et al., 2010). Studies conducted in other parts of South Africa have emphasised the importance of comprehensive investigations into the social dimensions of stress underlying co-morbid physical conditions and depression, to inform complex interventions (Roomaney et al., 2021). However, there is a need for more data to support region-specific interventions as these may differ between different primary healthcare areas. Thus, a study in the Western Cape province would continue to fill these gaps in the literature and provide valuable insights for addressing the disease burden within the province.

This study aims to contribute to the current understanding regarding the social determinants of depressive symptoms among patients with HIV and/or diabetes who receive chronic disease management in the Western Cape province of South Africa. This study also aims to understand if there is any variation in the depressive symptoms among patients with HIV and/or diabetes from different contexts, including variation explained by individual, household, and community level factors, within the Western Cape province.

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Part C: Manuscript

Social determinants of comorbid depression among patients living with diabetes and/or HIV at primary healthcare settings in Western Cape province of South Africa.

Proposed journal: BMC Psychiatry

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Abstract

Background: The co-occurrence of physical and mental health conditions poses a significant public health challenge, resulting in increased mortality and morbidity, reduced quality of life, and escalated healthcare utilisation and costs. Context-specific integrated responses are required to address the social determinants of co-occurring health conditions. This study aims to identify the determinants of depressive symptoms among patients with HIV and/or diabetes accessing healthcare at the primary health care level.

Methods: This study used baseline data collected from participants in a cluster randomised controlled trial, Project MIND, conducted in the Western Cape province of South Africa. The sample (N=1340) comprised participants diagnosed with HIV and/or diabetes. The study applied multi-level logistic regression analyses to examine factors associated with depressive symptoms at individual, household, and community levels.

Results: 1117 participants (83.36%) presented with moderate to severe depressive symptoms (567 living with HIV only, 447 with diabetes only, and 73 with HIV and diabetes). In a full model controlling for all explanatory variables at the individual-, household-, and community-levels, 34% and 31% of variance in depressive symptoms was explained by differences at the household-level and community-level respectively. Higher odds of moderate to severe depressive symptoms were significantly associated with being female (Odds Ratio (OR) = 2.57 [95% Confidence Interval (CI) = 1.57 – 4.21]), secondary level education (1.81 [1.07 – 3.04]), and food insecurity (1.80 [1.11 – 2.91]). Lower odds of moderate to severe depressive symptoms were associated with harmful/hazardous alcohol use (0.004 [0.00 – 0.001]), increased social support (0.96 [0.95 – 0.98]) and increased self-efficacy (0.93 [0.89 – 0.97]).

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Conclusion: This study highlights the significance of simultaneously considering individual, household and community levels when addressing co-occurring mental and physical health conditions in the Western Cape province of South Africa. These findings support policy decision-making and healthcare planning to address various levels of the context for effective interventions into mental and physical health condition co-occurrence.

Keywords: Depression, HIV, diabetes, chronic diseases, primary health care, South Africa

Background

The co-occurrence of diseases is a public health concern affecting one-third of the adult population in low- and middle-income countries (LMICs) (Nguyen et al., 2019). Co-occurring diseases have a negative impact on individuals and the health system, as they increase the risks of mortality and morbidity, reduce quality of life and productivity, and increase healthcare utilisation and expenditure (Arokiasamy et al., 2015, Bähler et al., 2015, Oni and Unwin, 2015, Salisbury et al., 2011, Glynn et al., 2011, Gijsen et al., 2001).

The co-occurrence of chronic physical and mental health conditions pose specific challenges to health systems. Studies have shown statistically significant associations between mental health disorders and the diagnosis of chronic physical conditions, particularly in more deprived groups (Scott et al., 2016, Barnett et al., 2012). Individuals with mental disorders are at a higher risk of developing chronic physical diseases (Daré et al., 2019, Arokiasamy et al., 2015, Stubbs et al., 2015, Yu et al., 2015) whilst individuals with chronic physical diseases are more likely to develop psychological conditions (Daré et al., 2019, Canadian Mental Health Association, 2008, Solano et al., 2006). While the global share of deaths attributable to NCDs has increased from 61% to 74% since 2000 (WHO, 2022), mental health conditions now account for 32.4% of Years Lived with Disability (YLDs), and for 13.0% of Disability-Adjusted Life Years (DALYs) (Vigo et al., 2016). Concurrently, LMICs remain faced with a large burden of communicable diseases which was responsible for approximately half of all deaths (46.8%) in 2019 (WHO, 2022). This disease burden is distressing as co-occurring mental disorders and chronic physical diseases are associated with more aggravating physical and mental health consequences (Daré et al., 2019).

South Africa faces a unique quadruple disease burden, including a high prevalence of communicable diseases; a growing rate of non-communicable diseases; high rates of deaths from injuries and violence; and highly prevalent neonatal, child, and maternal mortality (Meyiwa et al., 2014). The

prevalence of mental health disorders is also growing in South Africa, with more than one-third (38.5%) of the population experiencing at least one lifetime common mental disorders (Bantjes et al., 2019). This is exacerbated by the significant treatment gap that exists for mental healthcare in South Africa, as only one in four people receive appropriate treatment (Lund et al., 2010), as well as the barriers created by historically embedded geopolitical and socioeconomic contexts in which social and medical problems interplay in vulnerable population groups (Mendenhall et al., 2022).

The South African disease burden is marked by a significant prevalence of diabetes, HIV, and depression. With a high HIV prevalence of over 19% among adults aged 15 to 49, and approximately 270,000 new infections reported annually, the country remains a central focus of the HIV epidemic (Allinder and Fleischman, 2019). Additionally, the prevalence of diabetes has risen rapidly from 9% in 2015 to 11.3% in 2021, making it the highest prevalence in Africa despite an estimated 45.4% of diabetics remaining undiagnosed (International Diabetes Federation, 2021). Furthermore, more than a quarter of South African adults exhibit symptoms of probable depression, varying in severity across provinces and socio-demographic factors (Craig et al., 2022).

The co-occurrence of HIV, diabetes, and depression has been studied in previous research. There is strong evidence in Sub-Saharan Africa of a higher prevalence of depression among individuals living with HIV compared to the general population (Qubekile et al., 2022, Breuer et al., 2011, Ciesla and Roberts, 2001). While there are factors reducing depressive symptoms among individuals people living with HIV, such as longer knowledge of HIV status, longer ARV use, and social support structures (Pappin et al., 2012), depressive symptoms among people living with HIV is associated with slower rates of ART initiation, poor adherence, and worsened health outcomes (Truong et al., 2021). A meta-analysis of studies also indicates that individuals with depression have a 41% increased risk of type 1 diabetes and a 32% increased risk of type 2 diabetes (Yu et al., 2015). The underlying mechanisms of this relationship between depression and diabetes are not yet fully understood (Yu et al., 2015), although possible explanations include biological factors, such as altered neurotransmitter activity, heightened inflammation, and abnormalities in the hypothalamic-pituitary-adrenal axis (Harris, 2003, Duncan et al., 2003, Björntorp, 1991), behavioural factors, such as poor diet, physical inactivity, and substance abuse (Knol et al., 2007), and economic factors, such as poverty and limited access to nutritious foods (Bukhman et al., 2015, Agardh et al., 2011). Furthermore, there is strong evidence that suggests that the association between diabetes and depression is mediated by social contexts, especially in low-income countries (Lund et al., 2010).

In South Africa, research on the co-occurrence of HIV, diabetes, and depression have highlighted the influence of socioeconomic factors on the relationship between these conditions. Mendenhall and Norris (2015) found that women in Soweto who have diabetes often experience psychological distress, which worsens as the number of co-occurring physical conditions increases. The combination of psychological stress from living with diabetes, social circumstances, and sometimes the loss of a child to HIV affects the women's dietary choices and diabetes management, highlighting the impact of social and health concerns on illness experiences (Mendenhall and Norris, 2015). Another study conducted in South Africa revealed that a notable proportion of individuals with HIV and diabetes experienced symptoms of depression, which often went undiagnosed (Qubekile et al., 2022). The research failed to establish an association between the clinical features of HIV and diabetes and moderate to severe depressive scores. Instead, factors such as education level and gender among diabetic participants played significant roles in the manifestation of depressive symptoms (Qubekile et al., 2022). This may suggest that HIV or diabetes may not be the most pressing risk factors of depressive symptoms among individuals receiving healthcare for chronic diseases, but rather, other socio-demographic factors that drive depressive symptoms among this population group (Qubekile et al., 2022).

Taking the contextually dependent nature of co-occurring health conditions into account, health system responses need to be context-specific and move away from merely treating the biomedical complexities of co-occurring illnesses (Mendenhall et al., 2022). This notion is strongly supported by the World Health Organisation's (WHO) Conceptual Framework for Action on the Social Determinants of Health (CSDH framework) (Solar and Irwin, 2010). This framework highlights that social, economic, and political mechanisms influence population groups differently, which in turn shapes the determinants of the health of various population groups, their vulnerability to illness, and their access to healthcare (Solar and Irwin, 2010). The CSDH framework suggests that there are structural and intermediary determinants of illness which need to be considered for equitable healthcare delivery.

Ample research has focused on the socioeconomic determinants of co-occurring physical and mental health conditions, including population-specific demographic, socioeconomic, and cultural factors (Nguyen et al., 2019, Thienemann et al., 2019, Oni and Unwin, 2015). Structural determinants of co-occurring physical and mental health conditions highlighted in previous research conducted in South Africa include being of the female gender (Brady et al., 2022, Qubekile et al., 2022, Roomaney et al., 2021, van Coppenhagen and Duvenage, 2019), being part of marginalised ethnic groups (Brady et al., 2022, Roomaney et al., 2021), and individuals' socio-economic position, including lower levels of income (Pathirana and Jackson, 2018), lower individual education levels (Brady et al., 2022, Roomaney

et al., 2021, Chukwuedozie et al., 2021), and unemployment (Kamkuemah et al., 2022, Weimann et al., 2016, Alaba and Chola, 2013).

Intermediary determinants of co-occurring physical and mental health conditions in South Africa include material circumstances of living conditions, such as poor food availability (Petersen et al., 2019) and living in rural or urban areas according to the province in which the household is situated (Roomaney et al., 2021, Chukwuedozie et al., 2021). Biological and behavioural factors include age (Chang et al., 2019, Petersen et al., 2019b, Alaba and Chola, 2013), obesity (Roomaney et al., 2021, van Heerden et al., 2017, Shukla et al., 2014), smoking (Alaba and Chola, 2013), and treatment adherence (Folb et al., 2015). Relevant psychosocial factors include relationship status (Mukadas and Ushotanefe, 2021, Roomaney et al., 2021), social stress (Schmidt-Sane et al., 2023), social support (Mendenhall et al., 2022, Bosire, 2021), and self-efficacy (Closson et al., 2018, Wagner et al., 2017). Health system factors have also been shown to create major barriers to healthcare access, such as affordability, availability, and acceptability of care, which often underscore the disparities in health outcomes between different groups in South Africa (Gordon et al., 2020).

The majority of the studies conducted in South Africa exclusively examine the variability in outcomes of patients with co-occurring physical and mental health conditions associated with individual-level factors. Therefore, the potential influence of contextual factors across multiple population levels, encompassing household and community levels, have not been investigated in this context. While previous studies have acknowledged variations in chronic disease and depressive symptom prevalence across different provinces and districts in South Africa (Asare et al., 2022, Craig et al., 2022, Weimann et al., 2016, Lund et al., 2010), these studies either focused solely on a single specific level (such as individual or district levels) or failed to report the variations attributable to distinct contextual levels. Effective policymaking requires information on the degree to which variation in chronic disease outcomes is linked to contextual factors at population levels beyond the individual (Mishra, 2019).

This study sought to understand how the determinants of depressive symptoms among persons living with HIV and/or diabetes at the individual level are simultaneously nested within the different contextual levels of influence, including the household and community levels, in the Western Cape province of South Africa. In addition to demographic factors, structural and intermediary determinants of health, including household socioeconomic status and psychosocial, environmental and health system factors were investigated. The Commission on Social Determinants of Health (CSDH) model was used to guide this analysis.

Methods

Study setting

This study uses data collected at the baseline assessment of Project MIND. Project MIND was co-designed between the Western Cape Department of Health (WCDoH), the South African Medical Research Council (SAMRC), the University of Cape Town, and Oxford University (Myers et al., 2018). Project MIND set out to determine the effectiveness and cost-effectiveness of the collaborative care models for integrated mental health and chronic disease care, as well as to test which of these models of care most effectively improve mental health and chronic disease outcomes by means of a three-arm, cluster randomised controlled trial (cRCT) (Myers et al., 2018). The WCDoH purposively selected 24 primary healthcare (PHC) clinics which offered co-located HIV and diabetes services (including 15 urban and 9 rural sites) in order to adequately represent the provincial distribution of PHC clinics which are located in geographically distinct catchment areas and serve different populations in the different health districts (Myers et al., 2018).

Study participants

Participants of Project MIND were enrolled between 1 May 2017 and 31 March 2019 (Myers et al., 2022). The eligibility criteria for enrollment included taking medication for diabetes (Type 1 or Type 2) or antiretroviral therapy (ART) for HIV at the time of the study, being at least 18 years of age, and having depressive symptoms (Center for Epidemiology Scale on Depression (CES-D) score ≥ 16) or hazardous/harmful alcohol use (Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8) during the screening process (Myers et al., 2018). The sample size required to meet the inference requirements of Project MIND was calculated as eight clinics per arm (24 HIV and 24 diabetes services in total), with a cluster size of 25 participants per service (600 participants from HIV and 600 participants from diabetes clinics) (Myers et al., 2018). 1340 participants (801 with HIV; 622 with diabetes) were enrolled in the Project MIND and participated in the baseline assessment (Myers et al., 2022).

Variables of the study

Dependent variable

Depressive symptomatology was measured by means of the Center for Epidemiologic Studies Depression Scale (CES-D). The 20-item CES-D measures depressive behaviours and feelings during the previous week, with higher scores indicating more severe symptoms of depression (Radloff, 1977). Standard cut-off points were used in Project MIND to categorise participants' depressive symptoms as no to mild depression (score 0-15), moderate depression (score 16-23), and severe depression (24-60).

The dependent variable of this study is a binary categorical variable of participants' depressive symptoms indicating: (1) no to mild depressive symptoms (CES-D score < 16) and (2) moderate to severe depressive symptoms (CES-D score ≥ 16).

Independent variables

Structural determinants

Structural determinants included ethnicity, education, income, and employment status (Solar and Irwin, 2010). Ethnicity was dichotomised as a binary variable as (1) Black African and (0) other (including Coloured, Asian/Indian and White categories). Employment included informal and formal employment and was dichotomised as a binary variable as (1) employed and (0) not employed (including unemployed: looking for work or not, and pensioner or student/scholar). Education was measured in years of schooling and categorised as (1) primary school or less completed, (2) some high school years completed and (3) high school completed and/or further studies. Household income was measured in five categories. An interval regression was used to generate a continuous income variable using age, gender, race, and employment status as covariates. Furthermore, asset index was derived through the application of multiple correspondence analysis (MCA) based on housing characteristics (e.g., type of wall, roof, etc), ownership of assess (e.g. TV, fridge, car, etc), and access to utilities (e.g. source of drinking water and toilet facilities). The wealth index is used to categorise participants into five distinct wealth quintiles .

Intermediate determinants

Intermediate determinants included biological, behavioural, and psychosocial factors, as well as material circumstances and health system factors (Solar and Irwin, 2010). Biological factors included age and gender. Age was measured in single years from 18 years and included in the analysis as a continuous variable. Gender was dichotomised as a binary variable as (1) female and (0) male.

Behavioural factors included smoking, harmful/hazardous alcohol use, body mass index (BMI), and HIV and diabetes medication adherence. Smoking was included as a categorical variable indicating (0) never smoke, (1) ex-smoker, and (2) current smoker. Alcohol consumption and drinking behaviours were measured by means of the 10-item Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001). Standard cut-off points were used in Project MIND to categorise participants' alcohol use as no drinking (AUDIT score of 0), low risk drinking (scores 1-7), hazardous drinking (scores 8-15), and harmful drinking (scores ≥16) (Babor et al., 2001). AUDIT scores were included in the analysis as a

binary variable as (1) hazardous (including hazardous (scores 8-15) and harmful drinking (scores 16 or more)) and (0) low risk (including no drinking and low risk drinking (scores <8)).

Adherence data was collected by means of the Center for Adherence Support Evaluation (CASE) Adherence Index during the Project MIND baseline assessment to measure HIV and diabetes medication adherence respectively. This composite measure consists of three central questions concerning adherence: frequency of missed medication doses, difficulty taking medication on time, and time since the most recent missed dose (Mannheimer et al., 2006). Standard cut-off points were used in Project MIND and in this study to categorise participants' adherence as (1) good adherence (score>10) and (0) poor adherence (score ≤10). The adherence scores for patients with HIV and diabetes were combined to create one adherence variable. Obesity was calculated from the weights and heights of respondents as weight (measured in kilograms) divided by height (meters) squared. A binary variable was generated as (1) obese (including BMI scores > 30) and (0) not obese (including BMI scores for individuals classified as underweight (<18.6), normal weight (18.6-24.9), and pre-obesity (25.0-29.9)).

Psychosocial factors included relationship status, social support and self-efficacy. Relationship status was dichotomised as a binary variable as (1) single (including widow/widower, divorced or separated, and never married) and (0) not single (including married and living with partner). Social support was measured by the Medical Outcomes Study (MOS) Social Support survey, which is a 19-item self-assessment tool with subscales of support, including emotional/informational, tangible, affectionate support, and positive social interaction (Sherbourne and Stewart, 1991). The items are scored between 1-5, creating a composite score. The composite score was transformed in the Project MIND baseline data to give a score between 0-100. Self-efficacy was measured using the Social Problem-Solving Inventory-Revised: Short Form (25-item self-report questionnaire) which is used to determine participants' functional problem-solving skills. Higher scores in the negative problem orientation, impulsivity-carelessness style and avoidant style on the Social Problem-Solving Inventory reflect a more maladaptive approach to problem solving (Hawkins et al., 2009). Higher scores on the positive problem orientation and rational problem solving on the Social Problem-Solving Inventory indicate more adaptive problem solving (Hawkins et al., 2009). Self-efficacy and social support scores were included as continuous variables.

Material circumstances included housing stability, food insecurity, and average household expenditure. Housing stability was dichotomised as (1) housing stability and (0) housing instability.

Food insecurity was dichotomised as (1) yes (including seldom, sometimes and often) and (0) no. The average household expenditure was coded into 9 categories. A continuous household expenditure variable was generated using lower and upper income limits and fitting an interval regression model to predict monthly household expenditure (using the independent variables age, gender, race, and employment status). Health system factors included PHC site location and total out-of-pocket expenditure. PHC location site was used as binary variable as (1) urban and (2) rural.

Data analysis

The analysis was done using Stata version 17 for MacOS. Descriptive analysis was conducted to summarise the baseline characteristics using mean (n) and standard deviation (SD) for continuous variables and frequency (n) and percentage (%) for categorical variables.

This study set out to examine the predictors of depressive symptoms in patients living with HIV and/or diabetes at the baseline of Project MIND. Multi-level regression was used to assess the variation in the baseline depressive symptoms in patients living with HIV and/or diabetes across households and different communities included in Project MIND. The binarised variable for depressive symptoms was used for the multi-level logistics regression. Multi-level regression was used for the analysis as this method allowed partitioning the variation of depressive symptoms into factors attributable to various levels of influence, including individual, household and context-related factors, on patients' experience of depressive symptoms (Leyland and Groenewegen, 2020). This approach is appropriate considering the main premise of the CSDH framework, that differences between individuals' health and the population average can be attributable to the differences in their contextual realities, in part, as well as to the individual differences within different contexts (Solar and Irwin, 2010).

This multi-level analysis used a three-level pyramid structure with chronic disease patients with depressive symptoms at the lowest level (level one), nested within the household-level (level two), nested within the community at the highest level (level three). The PHC sites served as a proxy for community-level influences in this analysis.

Random intercepts were added in the multi-level model at the household and community levels, using the grouping variables of household socioeconomic status (level two) and PHC catchment areas (level three) for each respective level. Random intercepts account for the unobserved or unmeasured heterogeneity that exists across the different levels of the data hierarchy, allowing the intercept (the constant term) to vary across the levels (Leyland and Groenewegen, 2020). Thus, the random intercept

model allowed for the possibility that depressive symptoms may vary between different households and between different PHC catchment areas (or communities), after accounting for the individual differences. Individual-, household-, and community-level predictors were sequentially added in the multi-level model with random intercepts. The individual level (level one) predictors included age, gender, ethnicity, relationship status, education, employment status, smoking, obesity, alcohol use behaviours, medication adherence, self-efficacy, and social support. The household level (level two) predictors included housing stability and food insecurity. The community level (level three) predictors included the urban/rural status of the PHC catchment areas.

Four random intercept multi-level models were fitted sequentially. Model 1 was fitted only with the random intercepts for the levels of the PHC-catchment areas (Level 3) and household socioeconomic status (Level 2) without additional predictors. The overall depressive symptoms are modelled as the sum of the intercept (β0) and the error term (ε). Model 1 can expressed as follows:

$$DepSympt_{ijk} = \beta_0 + u_k + v_{jk} + e_{ijk}$$

where $DepSympt_{ijk}$ is the depression status (as measured by CES-D score) of participant i in household j attending PHC k. β_0 is the mean CES-D across all participants. u_k, v_{jk}, e_{ijk} respectively measure the residuals at PHC-level, household-level and individual level.

Model 2 was fitted with the random intercepts using the grouping variables for Level 2 (household socioeconomic status) and level 3 (PHC-catchment area), as well as the individual-level predictors. The overall depressive symptoms are modelled as the sum of the intercept (β0), the effect of individual-level predictors (β1 - β13), and the error term (ε). Model 2 can be expressed as follows:

$$\begin{aligned} DepSympt_{ijk} = \beta_0 + \beta_1 age_{ijk} + \beta_2 gender_{ijk} + \beta_3 race_{ijk} + \beta_4 relationship\ status_{ijk} \\ + \beta_5 education_{ijk} + \beta_6 employment_{ijk} + \beta_7 smoking_{ijk} + \beta_8 obesity_{ijk} \\ + \beta_9 hazardous\ alcohol\ use_{ijk} + \beta_{10} obesity_{ijk} + \beta_{11} adherence_{ijk} \\ + \beta_{12} self\ efficacy_{ijk} + \beta_{13} social\ support_{ijk} + u_k + v_{jk} + e_{ijk} \end{aligned}$$

where $DepSympt_{ijk}$ is the depression status (as measured by CES-D score) of participant i in household j attending PHC k. β_0 is the mean CES-D across all participants. $\beta_1 - \beta_{13}$ measure the regression coefficients for each individual-level predictor variable, holding all other variables constant. u_k, v_{jk}, e_{ijk} respectively measure the residuals at PHC-level, household-level and individual level.

Model 3 was fitted with the random intercepts for Level 2 and 3, as well as the individual-level and household-level predictors. The overall depressive symptoms are modelled as the sum of the intercept (β0), the effects of individual-level predictors (β1- β13), the effects of household-level predictors ($\gamma_1 - \gamma_2$), and the error term (ε). Model 3 can be expressed as follows:

$$\begin{aligned} DepSympt_{ijk} = {} & \beta_0 + \beta_1 age_{ijk} + \beta_2 gender_{ijk} + \beta_3 race_{ijk} + \beta_4 relationship\ status_{ijk} \\ & + \beta_5 education_{ijk} + \beta_6 employment_{ijk} + \beta_7 smoking_{ijk} + \beta_8 obesity_{ijk} \\ & + \beta_9 hazardous\ alcohol\ use_{ijk} + \beta_{10} obesity_{ijk} + \beta_{11} adherence_{ijk} \\ & + \beta_{12} self\ efficacy_{ijk} + \beta_{13} social\ support_{ijk} + \gamma_1 housing\ stability_{jk} \\ & + \gamma_2 food\ security_{jk} + u_k + v_{jk} + e_{ijk} \end{aligned}$$

where $DepSympt_{ijk}$ is the depression status (as measured by CES-D score) of participant i in household j attending PHC k. β_0 is the mean CES-D across all participants. $\beta_1 - \beta_{13}$ measure the regression coefficients for each individual-level predictor variable, holding all other variables constant. $\gamma_1 - \gamma_2$ measure the regression coefficients for each household-level predictor variable, holding all other variables constant. u_k, v_{jk}, e_{ijk} respectively measure the residuals at PHC-level, household-level and individual level.

Model 4 was fitted with the random intercepts for Level 2 and 3, as well as the individual-, household- and PHC-level predictors. The overall depressive symptoms are modelled as the sum of the intercept (β0), the effects of individual-level predictors (β1- β13), the effects of household-level predictors ($\gamma_1 - \gamma_2$), the effects of PHC-level predictors (α_1), and the error term (ε). Model 4 can be expressed as follows:

$$\begin{aligned} DepSympt_{ijk} = {} & \beta_0 + \beta_1 age_{ijk} + \beta_2 gender_{ijk} + \beta_3 race_{ijk} + \beta_4 relationship\ status_{ijk} \\ & + \beta_5 education_{ijk} + \beta_6 employment_{ijk} + \beta_7 smoking_{ijk} + \beta_8 obesity_{ijk} \\ & + \beta_9 hazardous\ alcohol\ use_{ijk} + \beta_{10} obesity_{ijk} + \beta_{11} adherence_{ijk} \\ & + \beta_{12} self\ efficacy_{ijk} + \beta_{13} social\ support_{ijk} + \gamma_1 housing\ stability_{jk} \\ & + \gamma_2 food\ security_{jk} + \alpha_1 urban_k + u_k + v_{jk} + e_{ijk} \end{aligned}$$

where $DepSympt_{ijk}$ is the depression status (as measured by CES-D score) of participant i in household j attending PHC k. β_0 is the mean CES-D across all participants. $\beta_1 - \beta_{13}$ measure the regression coefficients for each individual-level predictor variable, holding all other variables constant.

$\gamma_1 - \gamma_2$ measure the regression coefficients for each household-level predictor variable, holding all other variables constant. α_1 measures the regression coefficient for the community-level predictor variable, holding all other variables constant. u_k, v_{jk}, e_{ijk} respectively measure the residuals at PHC-level, household-level and individual level.

The regression model produced partial regression coefficients to show the effect of a unit change of a single independent variable on depressive symptoms net of the other variables. The results of the regression analyses were reported as odds ratios with the respective 95% confidence intervals (CIs) of each to signify precision. Significance was set at $p<0.05$. The estimated intraclass correlation coefficients (ICCs) were used to unpack the proportion of the variance of the outcome (depressive symptoms) attributable to the grouping- and individual-level variables respectively and was used to calculate the extent to which the variance of total depressive symptoms can be attributed to the differences between the PHC catchment areas (communities) and differences between the socioeconomic statuses of households nested within each PHC site grouping. A high ICC suggests that the random effects (group-level random intercepts) contribute significantly to the variability in the dependent variable, to determine whether there are meaningful group differences. Additionally, the likelihood ratio test was performed to compare the goodness of fit of the different multi-level logistic models. The test compares the log-likelihoods of between two models with a statistically significant result indicating that the more complex model (with additional predictors) provides a significantly better fit than the simpler model (Wu and Vos, 2018). The Akaike's information criterion (AIC) and Bayesian information criterion (BIC) were used for model selection. Lower AIC and BIC values indicate better model fit (Wu and Vos, 2018).

Results

Socio-demographic and economic characteristics of study participants

The socio-demographic characteristics, household circumstances, and community level factors are summarised in Table 1. Of the study participants (n=1340), 223 participants (16.64%) presented with no to mild depressive symptoms (151 living with HIV only, 62 with diabetes only, and 10 with HIV and diabetes) and 1117 participants (83.36%) presented with moderate to severe depressive symptoms (567 living with HIV only, 447 with diabetes only, and 73 with HIV and diabetes). The mean CES-D score (Standard Deviation – SD) among the participants was 26.77 (12.02). Participants had a mean age (SD) of 45.50 (12.78) years. The majority of the participants were female (n=1019; 76.04%), part of the Black African racial group (n=807; 60.22%), single (n=814; 61.02%), and unemployed (n=918; 68.51%). Participants had varying levels of education. While a third of participants completed primary school or

less (n=437; 32.61%), half of the participants completed some years of high school (n=736; 54.93%) and a few (n=167; 12.46%) completed high school and/or further education. 34.55% of the participants were current smokers, 41.85% were classified as obese, and most participants presented either with harmful (28.69%) or hazardous (58.58%) drinking behaviours. Good adherence was reported by approximately two thirds of the participants (n=882; 65.92%), and respectively by 71.08% of participants taking medication for diabetes and 64.29% participants taking ARVs for HIV.

Psychosocial and clinical related characteristics of study participants

Participants reported a high mean (SD) of social support (72.66 (21.94)), although when considered according to CES-D scores, this mean was higher among participants with no to mild depressive symptoms (82.97 (18.15)) than among participants with moderate to severe depressive symptoms (70.61 (22.06)). The mean (SD) self-efficacy score was 27.32 (5.72). While 75.52% participants had a permanent place to stay, almost half of the participants (48.88%) reported food insecurity. The average (SD) predicted household income per month was R1584.10 (R610.61) and the average (SD) predicted household expenditure per month was R1520.69 (R348.41). Considering the community level factors, most PHC sites are in urban areas (n=855; 63.81%).

Table 1: Baseline characteristics of participants

	NO TO MILD DEPRESSIVE SYMPTOMS (N=223; 16.64%)			MODERATE TO SEVERE SYMPTOMS (N=1117; 83.36%)			TOTAL (N=1340)
	HIV only (n=151; 11.20%)	**DM only (n=62; 4.60%)**	**HIV and DM (n=10; 0.74%)**	**HIV only (n=567; 42.06%)**	**DM only (n=447; 35.39%)**	**HIV and DM (n=73; 5.42%)**	**Total**
CES-D score *	8.12 (4.78)	8.98 (5.29)	4.4 (4.65)	30.87 (9.42)	30.06 (9.05)	30.05 (9.38)	26.77 (12.02)
Age (years)	39.01 (10.22)	49.06 (12.75)	45.90 (11.80)	38.57 (9.98)	55.02 (10.55)	47.53 (7.98)	45.50 (12.78)
Gender							
Male	62 (4.63%)	34 (2.54%)	8 (0.59%)	115 (8.85%)	94 (7.01%)	8 (0.59%)	321 (23.96%)
Female	89 (6.64%)	28 (2.09%)	2 (0.15%)	452 (33.73%)	383 (28.58%)	65 (4.85%)	1019 (76.04%)
Ethnicity +++							
Black African	110 (8.21%)	25 (1.87%)	9 (0.67%)	380 (28.36%)	219 (16.34%)	64 (4.78%)	807 (60.22%)
Other	41 (3.06%)	37 (2.76%)	1 (0.07%)	187 (13.96%)	258 (19.25%)	9 (0.67%)	533 (39.78%)
Relationship status							
Single	110 (8.25%)	28 (2.10%)	3 (0.22%)	387 (29.01%)	236 (17.69%)	50 (3.75%)	814 (61.02%)
Not single	41 (3.07%)	34 (2.55%)	7 (0.52%)	177 (13.27%)	238 (17.84%)	23 (1.72%)	520 (38.98%)
Level of education							
Primary school completed or less	43 (3.19%)	24 (1.79%)	3 (0.22%)	141 (10.52%)	204 (15.22%)	22 (1.64%)	437 (32.61%)
Some high school years completed	80 (5.97%)	28 (2.09%)	6 (0.45%)	360 (26.87%)	222 (16.57%)	40 (2.99%)	736 (54.93%)
High school completed and/ or further studies	28 (2.09%)	10 (0.74%)	1 (0.07%)	66 (4.93%)	51 (3.81%)	11 (0.82%)	167 (12.46%)
Employment status							
Not employed	91 (6.79%)	35 (2.62%)	5 (0.37%)	396 (29.55%)	343 (25.59%)	48 (3.58%)	918 (68.51%)
Employed	60 (4.48%)	27 (2.01%)	5 (0.37%)	171 (12.76%)	134 (10.00%)	25 (1.87%)	422 (31.49%)
Smoking							
Never smoke	50 (3.73%)	18 (1.34%)	4 (0.30%)	291 (21.72%)	291 (21.72%)	54 (4.03%)	708 (52.84%)

Previous smoker	15 (1.12%)	12 (0.90%)	1 (0.07%)	49 (3.66%)	87 (6.49%)	5 (0.37%)	169 (12.61%)
Current smoker	86 (6.42%)	32 (2.39%)	5 (0.37%)	227 (16.94%)	99 (7.39%)	14 (1.04%)	463 (34.55%)
BMI							
Not obese	116 (8.66%)	43 (3.21%)	4 (0.30%)	398 (29.70%)	183 (13.66%)	34 (2.54%)	778 (58.15%)
Obese	35 (2.61%)	19 (1.42%)	6 (0.45%)	167 (12.46%)	294 (21.94%)	39 (2.91%)	560 (41.85%)
Alcohol use **							
AUDIT: low risk	0 (0.00%)	0 (0.00%)	0 (0.00%)	52 (6.97%)	36 (4.83%)	7 (0.94%)	95 (12.73%)
AUDIT: hazardous	49 (6.57%)	30 (4.02%)	4 (0.54%)	91 (12.20%)	35 (4.69%)	5 (0.67%)	214 (28.69%)
AUDIT: harmful	102 (13.67%)	30 (4.02%)	6 (0.80%)	241 (32.31%)	47 (6.30%)	11 (1.47%)	437 (58.58%)
Case adherence index ‡							
Poor adherence	59 (4.41%)	25 (1.87%)	3 (0.22%)	214 (15.99%)	138 (10.31%)	17 (1.27%)	456 (34.08%)
Good adherence	92 (6.88%)	37 (2.77%)	7 (0.52%)	353 (26.38%)	337 (25.19%)	56 (4.19%)	882 (65.92%)
Social support §	81.83 (18.60)	84.26 (17.93)	92.21 (7.28)	69,11 (22.32)	71,95 (21.40)	73,42 (23.70)	72,66 (21.94)
Self-efficacy †	28.78 (5.19)	29.06 (4.74)	27.8 (4.78)	26,29 (5.69)	27,71 (5.85)	28,23 (5.75)	27,32 (5.72)
Housing stability							
Permanent place	102 (7.61%)	47 (3.51%)	9 (0.67%)	390 (29.10%)	410 (30.60%)	54 (4.03%)	1012 (75.52%)
No permanent place	49 (3.66%)	15 (1.12%)	1 (0.07%)	177 (13.21%)	67 (5.00%)	19 (1.42%)	328 (24.48%)
Food insecurity							
No	94 (7.01%)	52 (3.88%)	10 (0.75%)	234 (17.46%)	264 (19.70%)	31 (2.31%)	685 (51.12%)
Yes	57 (4.25%)	10 (0.74%)	0 (0.00%)	333 (24.85%)	213 (15.90%)	42 (3.13%)	655 (48.88%)
Average household income (R)	1600.90 (645.10)	1877.54 (668.09)	1878.39 (710.60)	1444.42 (609.34)	1700.33 (551.06)	1585.11 (607.70)	1584.10 (610.61)
Average household expenditure (R)	1522.58 (340.96)	1770.97 (338.36)	1600.90 (292.15)	1451.97 (340.97)	1591.73 (340.50)	1362.79 (276.58)	1520.69 (348.41)
Areas of PHC							
Urban study site	78 (5.82%)	25 (1.87%)	4 (0.30%)	384 (28.66%)	315 (23.51%)	49 (3.66%)	855 (63.81%)
Rural study site	73 (5.45%)	37 (2.76%)	6 (0.45%)	183 (13.66%)	162 (12.09%)	24 (1.79%)	485 (36.19%)

Data are n (%) or mean (SD). *CES-D=Centre For Epidemiological Studies Depression Scale. **AUDIT=Alcohol Use Disorder Identification Test. ‡Self-reported adherence (%) to HIV and/or diabetes medication as measured on the CASE Adherence Index. § Self-reported social support (%) as measured by the MOS Social Support survey. † Self-efficacy as measured using the Social Problem-Solving Inventory-Revised. +++The category "ethnicity" in the table and regressions refers to a social construct based on race. Ethnicity was historically utilised during the Apartheid era in South Africa to confer disadvantages on certain groups. Race remains deeply interconnected with socio-economic factors, creating persisted inequities. This construct is also acknowledged in the CSDH framework as an important socioeconomic determinant of health.

Multilevel analysis

The extent of missing data was assessed prior to this analysis. Missing data was treated as missing at random and no imputation was performed, since the proportions of missing data were below 5% (Jakobsen et al., 2017). Ten missing values were deleted in total (missing data from adherence (2), obesity (2), and relationship status (6) variables). The final sample used in the analysis was therefore n = 1330. Highly correlated variables (correlation coefficient >0.6) included average household expenditure and average household income variables, which were subsequently excluded from the regression to prevent collinearity.

The results of the multi-level logistic regression (Models 1 – 4) are presented in Table 2. Intra-class correlation analysis of Model 1 (intercept only model) indicates that 31% and 24% of variance in depressive symptoms is explained by differences between the household- and community-levels respectively. This suggests that there is substantial variability in the odds of depressive symptoms among persons living with HIV and/or diabetes between communities and households. In model 2

(intercept model with individual-level covariates), individual-level factors that were significantly associated with having moderate to severe depressive symptoms included being female, having completed some high school years of education, harmful/hazardous alcohol use, increased self-efficacy, and social support. In Model 2, 37% and 34% of variance in depressive symptoms was explained by between-group differences between the household- and community- levels respectively.

Table 2: Results for the multi-level logistic regression model

	Model 1 Coeff. (SE)	Model 2 Coeff. (SE)	Model 3 Coeff. (SE)	Model 4 Coeff. (SE)
Age (years)		-0.00 (0.01)	-0.00 (0.01)	-0.00 (0.01)
Gender				
Male		ref	ref	ref
Female		0.97 (0.25)**	0.95 (0.25)**	0.94 (0.25)**
Race				
Other		ref	ref	ref
Black		-0.11 (0.31)	-0.17 (0.32)	-0.22 (0.32)
Relationship status				
Not single		ref	ref	ref
Single		-0.39 (0.24)	-0.42 (0.24)	-0.43 (0.24)
Level of education				
Primary school completed or less		ref	ref	ref
Some high school years completed		0.58 (0.26)**	0.60 (0.26)**	0.59 (0.26)**
High school completed and/or further studies		0.17 (0.37)	0.23 (0.37)	0.21 (0.37)
Employment status				
Unemployed		ref	ref	ref
Employed		-0.16 (0.24)	-0.03 (0.25)	-0.03 (0.25)
Smoking				
Never smoke		ref	ref	ref
Previous smoker		-0.27 (0.39)	-0.21 (0.39)	-0.21 (0.39)
Current smoker		-0.14 (0.25)	-0.19 (0.26)	-0.19 (0.26)
BMI				
Not obese		ref	ref	ref
Obese		0.22 (0.25)	0.25 (0.25)	0.25 (0.25)
Alcohol use				
Low risk		ref	ref	ref
Harmful/hazardous		-5.51 (0.75)**	-5.49 (0.75)**	-5.49 (0.75)**
Case adherence index ‡				
Poor adherence		ref	ref	ref
Good adherence		-0.05 (0.23)	-0.03 (0.23)	-0.02 (0.23)
Social support §		-0.04 (0.01)**	-0.04 (0.01)**	-0.04 (0.01)**
Self-efficacy †		-0.08 (0.02)**	-0.07 (0.02)**	-0.07 (0.02)**
Housing stability				
No permanent place			ref	ref
Permanent place			0.30 (0.26)	0.31 (0.26)
Food insecurity				
No			ref	ref
Yes			0.59 (0.25)**	0.59 (0.25)**
Areas of PHC				
Rural study site				ref
Urban study site				0.47 (0.60)
Variance components				
Household-level (L2) ICC (SE)	0.31 (0.07)	0.37 (0.09)	0.36 (0.09)	0.34 (0.09)
Community-level (L3) ICC (SE)	0.24 (0.07)	0.34 (0.09)	0.33 (0.09)	0.31 (0.09)

Intercepts of grouping variables				
Household-level (L2) variance (SE)	0.33 (0.16)	0.16 (0.21)	0.15 (0.21)	0.15 (0.21)
Community-level (L3) variance (SE)	1.13 (0.46)	1.81 (0.72)	1.67 (0.68)	1.57 (0.65)
Model fit				
AIC	1087.99	690.67	687.61	689.02
BIC	1103.56	778.95	786.28	792.88
Likelihood-ratio test				
LR Chi^2		425.32 ‡	7.05 ‡‡	0.59 ‡‡‡
Prob > Chi^2		0.00	0.03	0.44

Data is reported as regression coefficients (standard error). ** p≤0.05
‡Model 2 compared to model 1. ‡‡ Model 3 compared to model 2. ‡‡‡ Model 4 compared to model 3.

Model 3 (intercept model with individual- and household-level covariates) suggests that, in addition to the Level 1 variables identified in Model 2, the Level 2 predictor variable for food insecurity is significantly associated with higher odds of having moderate to severe depressive symptoms. Housing stability was not found to be a statistically significant predictor at this level. In Model 3, 36% and 33% of variance in depressive symptoms was explained by between-group differences between the household- and community-levels respectively. In Model 4, a full model fitted with the intercepts and controlling for all explanatory variables at the individual-, household-, and community-levels, the variables of Level 1 and 2 predictors mentioned above remained significantly associated, although the additional Level 3 variable comparing the urban/rural locations of the PHC area was not significantly associated with moderate to severe depressive symptoms. In Model 4, 34% and 31% of variance in depressive symptoms was explained by between-group differences between the household- and community-levels respectively.

Considering the goodness of fit of the four models, models 3 and 4 had the most appropriate fit based on lowest AIC and BIC values. In addition, the likelihood-ratio test (LR test) indicated a significant improvement in model fit (p-value < 0.05) when adding individual-level predictors (moving from Model 1 to 2), and when adding household-level predictors (moving from Model 2 to 3), although not when adding PHC site level predictors (moving from Model 3 to 4) (p=0.4428).

Factors associated with depressive symptoms

Table 3 shows the results of the multi-level logistic regression of factors associated with clinically significant depressive symptoms (CES-D score ≥ 16) among people living with HIV and/or diabetes as determined by Model 4 (a full model fitted with random intercepts and controlling for all explanatory variables at the individual-, household-, and community-levels). Model 4 was selected since there were no significant differences between the models 3 and 4 and both models offered comparable goodness of fit.

Among the socio-demographic variables, gender emerged as a significant predictor, with females exhibiting 157% (OR = 2.57 [95% CI = 1.57 – 4.21], p<0.00) higher odds of moderate to severe depressive symptoms compared to males. Increased age, being of the Black African group, and being employed was not statistically significantly associated (p>0.05) with lower odds of moderate to severe depressive symptoms.

Table 3: Multilevel logistic regression analysis of factors affecting depressive symptoms (Model 4)

	Odds ratio	Std. err	95% confidence interval
Age (years)	0.997	0.011	(0.976 – 1.018)
Gender			
Male (reference)	1		
Female	2.566**	0.252	(1.567 – 4.210)
Race			
Other	1		
Black	0.804	0.322	(0.425 – 1.513)
Relationship status			
Not single (reference)	1		
Single	0.653**	0.240	(0.409 – 1.044)
Level of education			
Primary school completed or less (reference)	1		
Some high school years completed	1.809**	0.265	(1.074 – 3.034)
High school completed and/or further studies	1.238	0.373	(0.596 – 2.566)
Employment status			
Unemployed (reference)			
Employed	0.970	0.249	(0.596 – 1.577)
Smoking			
Never smoke (reference)	1		
Previous smoker	0.812	0.394	(0.375 – 1.757)
Current smoker	0.828	0.256	(0.502 – 1.368)
BMI			
Not obese (reference)	1		
Obese	1.283	0.253	(0.781 – 2.109)
Alcohol use **			
Low risk (reference)	1		
Harmful/hazardous	0.004**	0.747	(0.000 – 0.001)
Case adherence index ‡			
Poor adherence (reference)	1		
Good adherence	0.979	0.226	(0.628 – 1.527)
Social support §	0.964**	0.007	(0.951 – 0.978)
Self-efficacy †	0.928**	0.024	(0.884 – 0.974)
Housing stability			
No permanent place (reference)	1		
Permanent place	1.358	0.259	(0.816 – 2.262)
Food insecurity			
No (reference)	1		
Yes	1.799**	0.246	(1.112 – 2.912)
Areas of PHC			
Rural study site (reference)	1		
Urban study site	1.595	0.599	(0.494 – 5.152)

** p≤0.05

Relationship status displayed a marginal impact on depressive symptoms. Single individuals had 35% (OR = 0.65 [95% CI = 0.41 – 1.04], p=0.07) lower odds of moderate to severe depressive symptoms compared to persons in a relationship. Educational attainment was another notable predictor. Participants who completed some high school years had 81% (OR = 1.81 [95% CI = 1.07 – 3.04], p=0.03) higher odds of having moderate to severe depressive symptoms compared those with primary school education levels. However, having completed high school and/or further studies did not significantly increase the odds of depressive symptoms.

Regarding individual behaviour-related variables, harmful/hazardous alcohol use exhibited a profound impact on participants' depressive symptoms. Individuals with harmful/hazardous alcohol use had 99.6% lower odds (OR = 0.004 [95% CI = 0.00 – 0.001], p<0.00) of moderate to severe depressive symptoms compared to participants with no to low risks of alcohol use. Medication adherence, obesity, and previously or currently smoking did not emerge as statistically significant predictors of depressive symptoms. The two psychosocial factors, self-efficacy and support, yielded statistically significant findings. Increased social support (OR = 0.96 [95% CI = 0.95 – 0.98], p<0.00) and self-efficacy (OR = 0.93 [95% CI = 0.88 – 0.97], p<0.00) were associated with lower odds of participants having moderate to severe depressive symptoms by 4% and 7% respectively.

Considering the material circumstances of the household, food insecurity compared to having food security was found to significantly increase the odds of having moderate to severe depressive symptoms by 80% (OR = 1.80 [95% CI = 1.11 – 2.91], p=0.02). Housing stability was found to be an insignificant predictor. Lastly, the PHC site area (urban or rural) was found to be an insignificant predictor of having moderate to severe depressive symptoms.

Discussion

This study highlights the importance of understanding the variability in depressive symptoms among patients with HIV and/or diabetes beyond individual-level factors. The study unveils three primary findings. Firstly, the results highlight that depressive symptom variance can be attributed to between-group differences. The results show that the proportion of depressive symptom variance can be explained by the differences between the household- and community-levels respectively. This could indicate that familial or household stressors as well as broader community-level factors may have a pronounced impact on the mental well-being of individuals with chronic diseases. Thus, individual, household, and community levels need to be considered concurrently for effective management of the co-occurring diseases. This corresponds with the findings of a significant body of previous research

in South Africa highlighting the critical role of social and community contexts in shaping the mental health outcomes of individuals living with chronic diseases (Roomaney et al., 2021, Mendenhall and Norris, 2015, Bukhman et al., 2015, Agardh et al., 2011, Lund et al., 2010).

Secondly, unlike the variance explained by the household level, which remained relatively stable despite the addition of covariates, variation in outcomes attributed to the community level increased after adding individual- and household-level covariates. This can be attributed to several factors. The stability in the variance explained by the household level may suggest that household dynamics and socioeconomic factors shared between households play a consistent role in influencing depressive symptoms. This stability may be indicative of the enduring impact of lifestyle, material, or environmental factors that are shared among individuals living in households with similar socioeconomic statuses (Kamkuemah et al., 2023, Mishra et al., 2019). The increase in variation attributed to the community level after adjusting for individual- and household-level factors could be a result of the complex interplay of contextual elements, including environmental aspects, social dynamics, or healthcare infrastructure that collectively shape the health outcomes within certain communities (Wang et al., 2023, Bachmann et al., 2022). For example, living in deprived compared to less deprived communities has been shown to affect the health of individuals differently due to differentials in exposure to violence, poverty, and access to nutrition (Kamkuemah et al., 2023, Suglia et al., 2016, Grafova et al., 2008). This result implies that variation in the observed depressive symptoms may be the result of clustering of shared social and environmental risk factors at the community level which is not fully captured by individual and household characteristics only.

This finding of the study echoes the calls for a paradigm shift to integrated healthcare management for chronic diseases in South Africa (Lebina et al., 2020, Myers et al., 2018, Roomaney et al., 2023). Integrated healthcare appreciates that social problems cluster with and affect medical problems, as well as that co-occurring diseases may be caused by different determinants and can present differently than singular disorders (Mendenhall et al., 2017). Whilst the Department of Health in South Africa has implemented an integrated chronic disease management model towards improved community-based service provision at the primary healthcare level (Department of Health, 2012), the fidelity of these interventions has greatly been influenced by contextual factors that vary between different contexts in the country (Ameh, 2020; Lebina et al., 2020). The variation in depressive symptoms at the household and community levels captured in this study alludes to the importance of including community-specific interventions into integrated healthcare approaches, in order to address the

unique socioeconomic factors that shape the co-occurrence of health conditions between different households in the same communities.

Thirdly, this study identified covariates at the individual, household and community levels which are significant determinants of depressive symptoms amongst chronic disease patients in the Western Cape province. These covariates include gender, education, alcohol use, social support, self-efficacy, and food insecurity. Firstly, the results of this study indicate an elevated prevalence of depressive symptoms among females which is in line with global trends (Violan et al., 2014) and previous research in South Africa (Brady et al., 2022, Qubekile et al., 2022, Roomaney et al., 2021, van Coppenhagen and Duvenage, 2019). This highlights the need for gender-specific mental health initiatives, although further investigations are warranted to unpack the reasons behind these gender differences. This may be related to biological, socioeconomic, environmental, or cultural factors which affect the health of women and men differently (Weimann et al., 2016, Verdonk and Klinge, 2012, Vlassoff, 2007), or may be attributed to the social roles, stress and depression levels, and lifestyle habits that differ between women and men (Chukwuedozie et al., 2021, van Coppenhagen and Duvenage, 2019). The historical differences in employment and educational opportunities and gender-based inequities in the health sector of South Africa may also largely explain this finding (Weimann et al., 2016). Therefore, gender-related differences should not be interpreted without consideration of the myriad of other factors underscoring the differing health of females compared to males in South Africa.

This study found an absence of a significant age effect on depressive symptoms, in contrast to various previous findings of increased age (Roomaney et al., 2021, Arokiasamy et al., 2015, Bähler et al., 2015, Barnett et al., 2012) and younger age groups (Thienemann et al., 2019, Alaba and Chola, 2013, Barnett et al., 2012) as significant determinants of co-occurring physical and mental health conditions. Previous research has found that whilst both younger and older groups may have similar odds of co-occurring diseases, their disease profiles may differ significantly (Chang et al., 2019). Older age groups have been shown to have higher odds of physical multimorbidity in South Africa, while younger groups experience more physical-mental health condition co-occurrence (Petersen et al., 2019). Future research may consider more nuanced examinations of age-related differences, possibly through the adoption of finer age stratifications and the inclusion of a wider range of physical and mental health conditions to unpack the unique needs of distinct age cohorts.

Education also emerged as a key determinant. This study revealed an unexpected association between secondary school education and an increased likelihood of experiencing moderate to severe

depressive symptoms. This finding contrasts with previous research emphasizing the link between lower educational attainment and the co-occurrence of physical and mental health conditions (Brady et al., 2022, Roomaney et al., 2021, Chukwuedozie et al., 2021). It is plausible that individuals with a secondary level education might possess a heightened ability to recognize and articulate their emotional states or identify depressive symptoms compared to persons with lower levels of education. The curriculum at the secondary level of schooling might also change individuals' knowledge, attitude, and awareness about mental health, leading to an increased perception and reporting of depressive symptoms in this group (Lee et al., 2023). Future research should delve into the specific contextual factors that might mediate or moderate this relationship.

The unexpected observation that individuals with harmful/hazardous alcohol use had significantly lower odds of experiencing moderate to severe depressive symptoms compared to those with no to low risks of alcohol use contradicts previous research findings (Mpinganjira et al., 2023, Mishra et al., 2021). Firstly, it is possible that participants with harmful/hazardous alcohol use may use alcohol as a coping mechanism (albeit unhealthy) which could have mitigated their experience of depressive symptoms. The psychological or physiological effects of alcohol use may temporarily mask or suppress depressive symptoms, leading to a lower reported likelihood of experiencing such symptoms (Choi et al., 2014). Secondly, societal norms and values related to alcohol consumption may create an environment that facilitates socialisation and reduces social isolation, which could contribute to the reported lower risk of experiencing depressive symptoms (Choi et al., 2014). Furthermore, previous research suggests that patients may favour expenditure on alcoholic beverages, which displaces their expenditure on healthcare and reflects a neglect of healthcare needs (Mutyambizi-Mafunda et al., 2023). Thus, the engagement in harmful/hazardous alcohol use may lead to patients' neglect of their mental health and underscore their lower reporting of depressive symptoms. It is essential to emphasise that these potential explanations do not negate the harmful consequences of excessive alcohol use on both mental and physical health in the long run (Morojele et al., 2012). Further research is warranted to delve deeper into this complex interplay between the context, individuals' engagement in harmful/hazardous alcohol use behaviours, and their experience of co-occurring depressive symptoms.

The influence of psychosocial factors, such as self-efficacy and social support, on reduced depressive symptoms found in this study aligns with previous research in South Africa (Mukadas and Ushotanefe, 2021, Roomaney et al., 2021, Closson et al., 2018, Wagner et al., 2017). These factors likely act as buffers against stress and adversity, enabling individuals with chronic diseases to cope more effectively

through fostering resilience (Wicke et al., 2014, Schmidt-Sane et al., 2023). Improved coping abilities and a sense of control over one's circumstances can lead to a more positive outlook and better emotional regulation, lowering the likelihood of experiencing depressive symptoms. Studies have also highlighted the positive impact of self-efficacy on chronic disease education, self-management and self-care practices, and on reducing distress and depression often associated with chronic diseases (Devarajooh and Chinna, 2017, Kav et al., 2017, Nokes et al., 2012). Likewise, robust social support networks provide emotional and tangible assistance, fostering a sense of belonging and security, and thereby mitigating the negative impact of stress and promoting overall psychological well-being (Jiao et al., 2021, Singer et al., 2019). Access to resources and healthy coping strategies through social support can also reduce feelings of isolation and loneliness often linked to living with a chronic physical disease (Cantarero-Prieto et al., 2018). These findings highlight the potential role of self-efficacy and social support in fostering empowerment and improving mental health outcomes, particularly in the context of chronic illness.

The significant association between food insecurity and heightened odds of depressive symptoms among chronic disease patients found in this study could be explained by the profound impact of inadequate access to nutritious and sufficient food on psychological well-being (Ae-Ngibise et al., 2021). Previous research in South Africa has established a strong correlation between household food insecurity, depression, and alcohol misuse in individuals with chronic physical diseases (Petersen et al., 2019). The stress, uncertainty, and psychological strain induced by insufficient access to food resources might contribute to an increased vulnerability to experience depressive symptoms (Lemke et al., 2003). Conversely, the absence of a significant association between obesity and depressive symptoms observed in the study contradicts pervious research on this topic (Alaba and Chola, 2013, Roomaney et al., 2021). The intricate relationship between obesity and mental health could be influenced by cultural norms and perceptions surrounding body image and weight, which may vary across different populations and socioeconomic contexts. Research has found that the cultural acceptance of overweight and obesity as symbols of prosperity and well-being is prevalent in various African countries, including South Africa, which perpetuates the idea that being overweight signifies access to abundant food and resources (Simfukwe et al., 2017). Furthermore, the notion that obesity is linked to happiness may lead to comfort eating and subsequent weight gain, making it an obesogenic factor in certain societies (Muda et al., 2015).

Another explanation is that there may not be a linear relationship between socioeconomic status, health, and obesity in South Africa where inequality, undernutrition, and obesity co-exist. Rather, this

association may follow a social gradient where inequities and vulnerabilities are compounded in disadvantaged groups over the life course to affect physical and mental health outcomes (Kamkuemah et al., 2023). Thus, while food insecurity may create household stress, obesity may signal access to food (albeit perhaps unhealthy food sources) which reduces survival stress on patients with chronic diseases. Further research could be valuable to unpack this relationship in depth. However, this finding indicates that food availability, dietary choices, and the cultural understandings of nutrition may be important access points for policy interventions.

Limitations of the study

Interpretation of the findings is subject to limitations. First, the data is only from the Western Cape province, representing 11.9% of the total South African population according to the 2022 census (Statistics South Africa, 2022). The results can therefore not be generalised to all provinces. This analysis was also confined to the variables and population involved in the Project MIND trial. The Project MIND trial specifically enrolled individuals with HIV and/or diabetes who screened positive for depressive symptoms or harmful/hazardous alcohol use, making it impossible to compare the severity of depressive symptoms with patients who did not have HIV or diabetes but may have had other common chronic physical diseases, such as hypertension, or other common mental health symptoms, such as anxiety. This sampling limitation also meant there was an underrepresentation of persons without significant depressive symptoms in the sample. The cross-sectional analysis also limits any discussion of causality.

Another limitation of the study is that the data on which it is based was collected for the Project MIND trial between May 2017 and March 2019. This may limit the relevance of the results to the conditions in South Africa prior to the COVID-19 pandemic. The COVID-19 pandemic has significantly impacted the incidence and severity of diabetes and HIV, as well as in the rates of depression due to the direct and indirect effects of the pandemic. For example, Hong et al. (2023) found that people living with HIV reported high rates of mental health problems during the pandemic which were associated with increased psychological distress, substance use, and financial hardship, as well as with suboptimal medication adherence and antiretroviral therapy (ART) care engagement during the pandemic. The COVID-19 pandemic also disproportionately impacted specific demographics, including those with pre-existing chronic conditions such as diabetes (Khunti et al., 2022). COVID-19 had both direct and indirect detrimental effects on individuals with diabetes, with recurrent lockdowns and public health measures hindering access to routine diabetes care, delaying diagnosis, compromising self-

management, limiting follow-ups, and reducing access to medications (Khunti et al., 2022). These disruptions negatively affected lifestyle behaviours, emotional well-being and access to care.

People with chronic conditions might have experienced disruptions in their routine care, adherence to treatment, and lifestyle changes related to lockdowns and social distancing measures, which might have affected individuals' ability to manage their diabetes or access HIV treatment and mental health support, and thereby, impacted disease outcomes. For example, lockdown in South Africa was associated with increased utilization of the Centralized Chronic Medication Dispensing and Distribution (CCMDD) services by 10.8% for ARTs and 10.3% for non-communicable disease patients, although for patients receiving both ARTs and non-communicable disease medications, utilization of chronic medication distribution declined by 56.6%, with higher reductions occurred in lower socioeconomic status districts (Boachie et al., 2023). The pandemic also placed immense pressure on healthcare systems, potentially leading to changes in the availability and quality of care for chronic conditions. This strain could have affected how individuals with diabetes and/or HIV are managed and may have shifted healthcare resources away from routine care to pandemic-related needs. Pillay et al. (2021) found that access to public health services were limited in all provinces between March and December 2020, for example HIV testing (Pillay et al., 2021). These factors can affect how pre-pandemic data compares to the current incidence and severity of depression symptoms amongst persons living with chronic physical conditions.

Lastly, the pandemic has highlighted and, in some cases, widened health disparities. For example, Nwosu and Oyenubi (2021) examined income-related health inequalities in South Africa using data from pre-COVID-19 and COVID-19 periods. The authors found that poor health was pro-poor in the in both periods, with post-COVID-19 poor health being six times the value of the pre-COVID-19 period and that race, income, hunger, and employment were significant predictors of these inequalities (Nwosu & Oyenubi, 2021). Health disparities in South Africa shifted during and beyond the pandemic and therefore, data collected before COVID-19 may not fully address the increased need for equitable access to healthcare and the socioeconomic impacts on vulnerable populations. Future research may enhance the insights gained in this study for post-pandemic health system planning.

A strength of the collected data was that diabetes and HIV were measured and not self-reported, which eased judgement whether the diseases present in an individual were active or relevant. However, the data of socioeconomic, behavioural, psychosocial, and material factors were self-reported and therefore, subject to the limitations of self-reporting bias. Data on stigma and obstacles to accessing

healthcare was not collected, which limited the ability of this analysis to determine the impact of mental health or HIV stigma on depressive symptoms experienced by chronic disease patients. While this study was able to show the variance in depressive symptoms among chronic disease patients at household and community levels, this analysis did not include data to determine the variance related to the clinics where patients accessed healthcare, between different districts, or different provinces which limits this study from recommending macro-level policy interventions outside the Western Cape province.

Conclusion

This study highlights the significance of different population levels in shaping depressive symptoms among patients living with chronic diseases and necessitates simultaneous consideration of individual, household and community levels when addressing co-occurring mental and physical health conditions in the Western Cape province of South Africa. While the results of this study indicate covariates that are significant predictors of depressive symptoms among this population group, including gender, education, alcohol use, social support, self-efficacy, and food insecurity, the application of the multi-level model highlights that studying covariates at the individual, household or community levels in isolation may produce limited insights into the variation attributable to the different levels. The findings suggest that 34% and 31% of variance in depressive symptoms among patients with HIV and/or diabetes can be explained by differences at the household-level and community-level respectively. These findings are important for policy decision making and healthcare planning in South Africa, as it suggests that the management of co-occurring mental and physical health conditions require concurrent individual, household, and community-specific approaches in order to be effective.

Policy implications

Based on the study findings, integrated mental health and chronic disease care models remain of high priority. However, these models need to include comprehensive, context-specific interventions to address not only symptomatology, but also the different levels of the contexts in which ill-health unfolds. The results highlight that interventions should involve targeted support programmes for individuals from households with lower socioeconomic circumstances, as well as include initiatives that address inequalities between different communities and the socioeconomic conditions of households. For example, if neighbourhood safety is not prioritised, interventions promoting outdoor physical activity, healthcare access, or social engagement to improve both physical and mental health symptoms may be ineffective. Previous research has shown that urban planning and community development strategies are essential to not only improve health outcomes (Cummins et al., 2014), but

potentially also to ameliorate socioeconomic disparities in lower income communities (Thornton et al., 2016). These strategies should address the socioeconomic issues faced in communities through both participatory and community-engaged development programmes as well as policy-driven approaches. For example, initiatives such as skills training for local garden development, vocational training programmes, and peer support networks to foster community resilience should be accompanied by policy interventions that facilitate community safety, affordable access to healthcare, and healthy lifestyle choices (such as subsidies for healthy foods or increased taxes on alcohol and unhealthy foods). Interventions to foster partnerships between healthcare facilities, local authorities, and community-based organisations can also help create a network of mental health support that extends beyond clinical settings to address the specific needs of vulnerable populations in the community.

Furthermore, the results of this study highlight that interventions should focus on bolstering social support systems and self-efficacy, promoting mental health awareness from primary education years, and addressing household food insecurity. Policy initiatives should prioritise gender-sensitive health programmes and address the unique social and cultural contexts that contribute to gender-related differences in mental and physical health outcomes. Strengthening existing social support networks and establishing new community-based support systems that offer emotional, tangible, and informational assistance to individuals living with chronic diseases may foster a sense of belonging, social connectedness, and community engagement to mitigate the negative impact of stress and isolation on chronic disease patients. Such community-based approaches and health campaigns may incorporate integrated interventions that address harmful alcohol use, through the promotion of healthier coping mechanisms and providing effective support systems for individuals struggling with alcohol misuse. School-based interventions at the primary and secondary school levels could more explicitly raise awareness about mental health by teaching practical ways to maintain emotional and physical well-being, such as stress management and effective coping strategies, as well as instigate programmes that combat stigmatisation of mental illness, to help mitigate the likelihood of experiencing depressive symptoms later in life. Interventions to alleviate food insecurity can focus on establishing sustainable food assistance programmes and nutritional education initiatives, to ensure equitable access to nutritious and sufficient food resources and promote a healthy and balanced diet among individuals with chronic diseases.

Directions for future research

A natural progression from this study would be to perform similar analyses in different provinces, and to include municipality or district levels to the model in order to quantify the variation in depressive symptoms attributable to more macro-level contextual factors and ensure that appropriate policy interventions match the particular contextual realities. A similar research design to study other mental and chronic physical health conditions not included in this study – such as hypertension or anxiety – may elucidate whether the socioeconomic determinants identified in this study are relevant to the management of other co-occurring diseases in this context. This area of research would also benefit greatly from longitudinal studies which can unpack the cumulative effects of multi-level determinants on depressive symptoms in chronic disease patients.

With regards to the covariates identified in this study, further research is recommended to unpack the directionality of the relationship between the identified socioeconomic factors and depressive symptoms. For example, future analyses may explore the interactions between age, socioeconomic conditions, and gender-related difference to uncover the underlying mechanisms of the observed variability in depressive symptoms according to these factors. The relationship between depressive symptoms, the context, and individuals' engagement in harmful/hazardous alcohol use, their education level, and food insecurity versus obesity requires further inquiries to identify the most important entry points for policy interventions. Future research should also delve into the specific contextual factors that might mediate or moderate these relationships.

In addition, future research may also investigate covariates not included in this analysis. An important inquiry into the relationship between depressive symptoms and factors related to the hospitals or PHC clinics where chronic disease patients access healthcare may provide insights into how healthcare provision can be optimised for improved health outcomes. Household level variables not included in this analysis which can offer valuable insights include data on domestic violence, female- or child-headed households, household religious or cultural beliefs and stigma regarding HIV and mental health, household consumption patterns, and household size. Further community level covariates that may provide critical insights into the variation of depressive symptoms include community poverty levels, community attitudes, beliefs and myths, the impact of mass media exposure, the impact of community-level decision-making, neighbourhood safety, outdoor and recreational space access, and community violence. Overall, the findings of this study support the use of multi-level modelling in future research on the determinants of co-occurring diseases as it unfolds within various contexts, and this methodology is recommended to answer similar public health research questions.

Abbreviations

AUDIT: Alcohol Use Disorder Identification Test; CES-D: Centre for Epidemiology Scale on Depression; HIV: Human Immunodeficiency Virus; LMIC: Low- and Middle-Income Country; PHC: Primary Health Care; OOP: Out-of-pocket Payments; WHO: World Health Organisation

Authors' contributions

ST: Conceptualised the research protocol, study design, analysed the data and interpretation, and prepared the manuscript paper.

Funding

This study uses data from Project MIND. Project MIND is funded jointly by the British Medical Research Council, Wellcome Trust, Department for International Development, the Economic and Social Research Council, the Global Challenges Research Fund (MR/M014290/1). ST is a self-funded student in the Master of Public Health degree (Health Economics) at the University of Cape Town. The opinions presented in this publication are the sole responsibility of the authors and do not necessarily reflect the positions, policies, or perspectives of their respective institutions or funding partners.

Declarations

Ethics approval and consent to participate

Ethics approval for the study was granted by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC REF: 559/2023). Ethics approval for Project MIND was granted by The South African Medical Research Council, Cape Town, South Africa (EC004–2/2015), the University of Cape Town, Cape Town, South Africa (089/2015), and Oxford University, Oxford, UK (OxTREC_2–17). The current study was conducted in accordance with the Declaration of Helsinki ethical principles.

Data statement

Upon approval of a proposal and the signing of a data access agreement, a data dictionary and de-identified participant data can be accessed.

Requests can be made to bronwyn.myers-franchi@curtin.edu.au.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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PART D: Policy Brief

Social determinants of comorbid depression among diabetes and HIV/AIDS patients at primary healthcare settings in Western Cape Province of South Africa

Key messages

- The co-occurrence of physical and mental health conditions poses a public health challenge in South Africa, with depression among patients living with chronic physical conditions contributing largely to the healthcare burden.
- A multi-level analysis revealed that 34% and 31% of variance in depressive symptoms among patients with HIV and/or diabetes who access primary healthcare (PHC) clinics could be explained by differences at the household-level and community-level respectively.
- Higher odds of depressive symptoms were significantly associated with being female, having a secondary level education, and food insecurity.
- Lower odds of depressive symptoms were associated with harmful/hazardous alcohol use, increased social support, and increased self-efficacy.
- Policy interventions should address the socioeconomic factors related to households and communities to effectively address depressive symptoms among patients living with HIV and/or diabetes.

Introduction

This policy brief is directed to health policymakers in the Western Cape. In South Africa, 69.4% of the adult population live with two or more conditions, including combinations of cardiometabolic conditions (including diabetes), HIV and anaemia, and combinations of mental health disorders (Chang et al., 2019). Persons living with co-occurring physical and mental health conditions face an increased risk of mortality and morbidity, reduced quality of life, and escalated healthcare utilisation and costs.

A large treatment gap for mental health disorders exists, leading to only one in four people with a mental health disorder receiving treatment (Lund et al., 2010). Depression largely contributes to the health care burden in South Africa, as its prevalence in the general population is between 14% and 38% (Craig et al., 2022). Management of depression is complicated by its high co-occurrence with chronic diseases, including HIV and diabetes. Depression prevalence among people living with HIV in Sub-Saharan Africa ranges between 9% and 32% (Bernard et al., 2017). Depression prevalence among

diabetic patients has been estimated to be as high as 46.6% in South Africa (Jansen van Vuuren and Pillay, 2019).

Socioeconomic determinants of co-occurring physical and mental health conditions differ between different contexts. It is essential to unpack the socioeconomic factors associated with depressive factors among patients with HIV and/or diabetes related to different contexts, including understanding factors related to the household and differences between communities. This is critical for effective policy development and healthcare planning.

This study investigated the social determinants of depressive symptoms among patients living with HIV and/or diabetes at the hierarchical levels of individual, household, and community among patients who receive chronic disease management at PHC clinics in the Western Cape province of South Africa.

How the study was conducted

This study used baseline data collected from participants in a cluster randomised controlled trial, Project MIND, conducted in the Western Cape province of South Africa. The study setting included 24 PHC clinics which offered co-located HIV and diabetes services (including 15 urban and 9 rural sites) (Myers et al., 2018). The sample (N=1340) comprised participants diagnosed with HIV and/or diabetes.

The study applied a multi-level logistic regression analysis to study factors associated with depressive symptoms at individual, household, and community levels based on the Commission on Social Determinants of Health model (Solar and Irwin, 2010). The dependent variable was participants' depressive symptoms as measured by the Center for Epidemiologic Studies Depression Scale. Independent variables included: (1) structural determinants, including ethnicity, education, income, and employment status; (2) intermediate determinants, such as biological, behavioural, and psychosocial factors, as well as material circumstances of the household; and (3) factors related to the PHC sites (communities) where patients accessed care.

Multi-level regression was used to partition the variation of depressive symptoms attributable to various levels of influence (Leyland and Groenewegen, 2020). A three-level pyramid structure was used with chronic disease patients with depressive symptoms at the lowest level (level one), nested within the household-level (level two), nested within the community at the highest level (level three). The PHC sites served as a proxy for community-level influences.

Main findings

- 1,117 of the participants (83,36%) presented with moderate to severe depressive symptoms (567 living with HIV only, 447 with diabetes only, and 73 with HIV and diabetes).
- In a model controlling for all explanatory variables at the individual-, household-, and community-levels, 34% and 31% of variance in depressive symptoms was explained by differences at the household-level and community-level respectively.
- Higher odds of moderate to severe depressive symptoms were significantly associated with being female, secondary level education, and food insecurity.
- Lower odds of moderate to severe depressive symptoms were significantly associated with harmful/hazardous alcohol use, increased social support, and increased self-efficacy.

Policy implications

The findings of this study highlight that individual, household and community level factors need to be considered when addressing co-occurring mental and physical health conditions. The Department of Health in the Western Cape should consider doing the following:

- Interventions should involve targeted support programmes for individuals from households with lower socioeconomic circumstances, as well as include initiatives that address inequities between different communities and the socioeconomic conditions of households.
- Policy initiatives should prioritise gender-sensitive health programmes and address the social and cultural contexts that contribute to gender-related differences in health outcomes.
- Strengthening existing social support networks and establishing new community-based support systems that offer emotional, tangible, and informational assistance to individuals living with chronic diseases may foster a sense of belonging, social connectedness, and community engagement to mitigate the negative impact of stress and isolation on chronic disease patients.
- Community-based approaches and health campaigns should incorporate integrated interventions that address harmful alcohol use, through the promotion of healthier coping mechanisms and providing effective support systems for individuals struggling with alcohol misuse.
- School-based interventions should more explicitly raise awareness about mental health by teaching practical ways to maintain emotional and physical well-being.
- Interventions to alleviate food insecurity can focus on establishing sustainable food assistance programmes and nutritional education initiatives, to ensure equitable access to nutritious and sufficient food resources and promote a healthy and balanced diet.

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Appendices

Appendix A: Descriptive statistics of the variables used in the analysis:

Variable	Overall sample (n=)	Chronic disease patients with no depressive symptoms (n=)		Chronic disease patients with clinically significant depressive symptoms (n=)	
		People with HIV	People with diabetes	People with HIV	People with diabetes
Age (years)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
(0) 18-29	n (%)	n (%)	n (%)	n (%)	n (%)
(1) 30-39	n (%)	n (%)	n (%)	n (%)	n (%)
(2) 40-49	n (%)	n (%)	n (%)	n (%)	n (%)
(3) ≥50	n (%)	n (%)	n (%)	n (%)	n (%)
Sex					
(0) Female	n (%)	n (%)	n (%)	n (%)	n (%)
(1) Male	n (%)	n (%)	n (%)	n (%)	n (%)
Race					
(0) African	n (%)	n (%)	n (%)	n (%)	n (%)
(1) Coloured	n (%)	n (%)	n (%)	n (%)	n (%)
(2) Other	n (%)	n (%)	n (%)	n (%)	n (%)
Relationship status					
(0) Single, separated or widowed	n (%)	n (%)	n (%)	n (%)	n (%)
(1) Significant other / married	n (%)	n (%)	n (%)	n (%)	n (%)
Level of education					
(0) Primary school or less	n (%)	n (%)	n (%)	n (%)	n (%)
(1) Some years of secondary school	n (%)	n (%)	n (%)	n (%)	n (%)
(2) Completed secondary school and/or further studies started	n (%)	n (%)	n (%)	n (%)	n (%)
Employment status					
(0) Unemployed	n (%)	n (%)	n (%)	n (%)	n (%)
(1) Employed	n (%)	n (%)	n (%)	n (%)	n (%)
Income					
(0) Quintile 1 (poorest)	n (%)	n (%)	n (%)	n (%)	n (%)
(1) Quintile 2 (less poor)	n (%)	n (%)	n (%)	n (%)	n (%)
(2) Quintile 3 (average)	n (%)	n (%)	n (%)	n (%)	n (%)
(3) Quintile 4 (less rich)	n (%)	n (%)	n (%)	n (%)	n (%)
(4) Quintile 5 (richest)	n (%)	n (%)	n (%)	n (%)	n (%)
Behavioural factors					
Drug use					
(0) No	n (%)	n (%)	n (%)	n (%)	n (%)
(1) Yes	n (%)	n (%)	n (%)	n (%)	n (%)
Obesity					
(0) Obese (BMI<30)	n (%)	n (%)	n (%)	n (%)	n (%)
(1) Not Obese (BMI≥30)	n (%)	n (%)	n (%)	n (%)	n (%)
Hazardous/harmful alcohol use					
(0) No	n (%)	n (%)	n (%)	n (%)	n (%)
(1) Yes	n (%)	n (%)	n (%)	n (%)	n (%)
Self-reported adherence >90%*	-	n (%)	n (%)	n (%)	n (%)
Poor disease control**					
(0) No	n (%)	n (%)	n (%)	n (%)	n (%)
(1) Yes	n (%)	n (%)	n (%)	n (%)	n (%)
Psychosocial circumstances (social support and social capital)					
Stressful life events***	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Social support****	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Problem-solving*****					
(0) Maladaptive style	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
(1) Adaptive style	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)

Material circumstances					
Housing stability (0) No (1) Yes	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)
Household food insecurity (0) No (1) Yes	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)
Type of dwelling (0) Formal (1) Informal	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)
Average household expenditure (0) <R1199 (1) R1200 – R5000 (2) >R5000	 n (%) n (%) n (%)	 n (%) n (%) n (%)	 n (%) n (%) n (%)	 n (%) n (%) n (%)	 n (%) n (%) n (%)
Health system factors					
Area of PHC *(0)* urban *(1)* rural	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)
Duration of visit (0) Collecting diabetes / ARV medication (1) Consulting with a health provider (2) Time to travel to the PHC	 Mean (SD) Mean (SD) Mean (SD)	 Mean (SD) Mean (SD) Mean (SD)	 Mean (SD) Mean (SD) Mean (SD)	 Mean (SD) Mean (SD) Mean (SD)	 Mean (SD) Mean (SD) Mean (SD)
Costs of access care *(0)* direct costs *(1)* indirect costs *(2)* income lost (for those employed)	 Mean (SD) Mean (SD) Mean (SD)	 Mean (SD) Mean (SD) Mean (SD)	 Mean (SD) Mean (SD) Mean (SD)	 Mean (SD) Mean (SD) Mean (SD)	 Mean (SD) Mean (SD) Mean (SD)

Data captured as mean and Standard Deviation (SD) (numerical variables) or frequency (n) and proportion (%) (continuous variables)
*Self-reported adherence (%) to either HIV, diabetes, or HIV and diabetes medication over last 30 days
**Poor disease control defined as HbA1c levels of 6.5 or more for diabetes and viral load of 1000 copies per mL or more for HIV
***Stressful life events: Higher scores on the Trauma History Questionnaire indicates a higher amount of exposure to traumatic events.
****Social support: Higher scores on the MOS social support survey scale, indicates higher levels of social support.
*****Problem-solving styles: Higher scores in the Negative problem orientation, Impulsivity-carelessness style and Avoidant style reflect a more maladaptive approach to problem solving (Hawkins et al., 2009). Higher scores on the Positive problem orientation and Rational problem solving indicate more adaptive problem solving (Hawkins et al., 2009).

Appendix B: Variable tables for data analysis

Table 1: Dependent variables

Dependent Variables	Scale	Categories
Depressive symptom (CES-D score)	Numerical – continuous	Mean (Standard Deviation) Coded from 9.1 of the baseline assessment Project Mind Codebook: BaseT_CESD_Cut_Off (total sample)

Table 2: Independent variables (Structural determinants)

Independent Variables	Scale	Categories
Race	Categorical – nominal	Coded from 2.6 of the baseline assessment: (0) African (1) Coloured (2) Other Project Mind Codebook: BaseT_Race
Level of education	Categorical – nominal	Coded from 2.10 of the baseline assessment: (0) Primary school or less (1) Some years of secondary school (2) Completed secondary school and/or further studies started Project Mind Codebook: BaseT_Education_Cat
Employment status	Categorical – nominal	Coded from 3.4 of the baseline assessment: (0) Unemployed: Coded from options of the baseline assessment: Unemployed and looking for work (3.4.1), Unemployed and not looking for work (3.4.2), Pensioner (3.4.6), Student/ Scholar/ Learner (3.4.7) (1) Employed: Coded from options of the baseline assessment: Employed part-time (3.4.3), Employed full-time (3.4.4), Self-employed (3.4.5) Project Mind Codebook: BaseT_Employ_Cat
Income (quintiles)	Categorical – ordinal	Household income will be categorically coded into 5 quintiles, ranging from the poorest to the richest quintile as given in the data set – coded from 3.7 of the baseline assessment (0) Quintile 1 (poorest) (1) Quintile 2 (less poor) (2) Quintile 3 (average) (3) Quintile 4 (less rich) (4) Quintile 5 (richest) Project Mind Codebook: BaseT_Income_Monthly_Average

Table 3: Independent variables (Intermediary determinants)

Independent Variables	Scale	Categories
Biological factors		
Age (years)	Numerical – continuous	Mean (Standard Deviation) Coded from 2.5 of the baseline assessment Project Mind Codebook: BaseT_Age
	Categorical – ordinal	Age will be categorically coded from 2.5 of the baseline assessment into age groups for ease of interpretation and specific information regarding age-group differences. (1) 18-29 (2) 30-39 (3) 40-49 (4) ≥50 Project Mind Codebook: BaseT_Age_category
Sex	Categorical – Binary	Coded from 2.4 of the baseline assessment: (0) Female (1) Male Project Mind Codebook: BaseT_Gender

Behavioural factors		
Hazardous alcohol use (AUDIT score)	Numerical – continuous	Mean (Standard Deviation) Coded from options 8.2, 8.5, and 8.8 – 8.14 of the baseline assessment

	Categorical – Binary	An AUDIT score ≥ 8 will be used to indicate hazardous/harmful alcohol use. Hazardous alcohol use will be categorically coded from options 8.2, 8.5, and 8.8 – 8.14 of the baseline assessment: (0) No (1) Yes Project Mind Codebook: BaseT_AUDIT_Cut_Off (total sample)
Obesity (BMI= kg/m2)	Categorical – Binary	A BMI greater than 30 is considered to be obese. Coded categorically from 2.2 and 2.3 of the baseline assessment: (0) Obese (BMI ≥ 30) (1) Not Obese (BMI < 30) Project Mind Codebook: Baseline_BMI
General self-efficacy	Numerical – continuous	Mean (Standard Deviation) Coded from the Generalised Self-efficacy Scale of the baseline assessment Project Mind Codebook: BaseT_SelfEfficacy_Composite
Self-reported adherence >90%	Three measures were used to assess adherence to HIV and diabetes treatment in the baseline assessment. The two measures that will be used in this analysis is: ● the AIDS Clinical Trials Group (ACTG) adherence questionnaire, coded from the baseline assessment: o For HIV: 6.67 – 6.86 ("other reasons" excluded) Project Mind Codebook: BaseT_percentage_adherent_ARVS_past_4days o For Diabetes: 7.75 – 7.94 ("other reasons" excluded) Project Mind Codebook: BaseT_DM_Case_ adherence_categories_DM ● the Visual Analog Scale (VAS), coded from the baseline assessment: o For HIV: 6.58 Project Mind Codebook: BaseT_VAS_HIV_adherence_categories o For Diabetes: 7.66 Project Mind Codebook: BaseT_VAS_DM_Adherence_categories This will be included as continuous variables and dichotomised using standard cut-off scores for adherence (≥ 90%)	
	Numerical – continuous	Mean (Standard Deviation)
	Categorical – binary	(0) No (< 90%) (1) Yes (≥ 90%)

Material circumstances		
Housing stability	Categorical – Binary	Coded from 3.2 of the baseline assessment: (0) No Coded from options of the baseline assessment: I'm living in a place but I may not be able to live there in the future (3.2.2) and I do not have any regular place where I can live (3.2.3) (1) Yes Coded from options of the baseline assessment: I have a place to live where I can stay as long as I want (3.2.1) Option: "other" will be excluded from the analysis Project Mind Codebook: BaseT_ Housing_instability
Type of dwelling	Categorical – Binary	Coded from 4.3 of the baseline assessment: (0) Formal dwelling: brick house, flat, retirement unit, townhouse, flatlet, worker's hostel Coded from options of the baseline assessment: 4.3.1, 4.3.3– 4.3.6, 4.3.9, 4.3.11 (1) Informal dwelling: traditional dwelling/hut, informal shack, tent/caravan Coded from options of the baseline assessment: 4.3.2, 4.3.7– 4.3.8, 4.3.10 Option: "other" will be excluded from the analysis. Project Mind Codebook: BaseT_HouseType
Household food insecurity	Categorical – Binary	Coded from 3.2 of the baseline assessment: (0) No (1) Yes Project Mind Codebook: BaseT_HHhunger.
Average household expenditure	Categorical – ordinal	Coded from 4.17 of the baseline assessment: (0) <R1199 Coded from options of the baseline assessment: 4.18.1 – 4.18.5 (1) Between R1200 – R5000 Coded from options of the baseline assessment: 4.18.6 – 4.18.8 (2) >R5000 Coded from options of the baseline assessment: 4.18.9 – 4.18.10 Option: "don't know" and "refuse" will be excluded from the analysis. Project Mind Codebook: BaseT_HHexpenditurerange

Health system factors		
Area of PHC	Categorical – Binary	Dichotomised into rural and urban categories from the data according to the area in which the PHC is situated (0) Metro: Mfuleni; Michael Mapongwana; KhayelitshaSite B; Nolungile; Nyanga; Gugulethu; Browns Farm; Macassar; Kraaifontein; Elsies River; Delft; Retreat, Hanover Park; Mitchells Plain; Crossroads. (1) Non-metro: Worcester; TC Newman; Ceres; Klawer; Lutzville; Vredendal; Grabouw; Hermanus; and Railton. Project Mind Codebook: BaseT_Site
Cost of access to chronic disease care	Numerical – continuous	(0) Direct costs: coded from 5.7, 5.11, 5.13, 5.15, 5.19 Project Mind Codebook: BaseT_Costsofclinicvisit_1-11 (1) Indirect costs: coded from 5.9, 5.17, 5.21, 5.23, 5.25 Project Mind Codebook: BaseT_Costsofclinicvisit_1-11 (2) Income lost: coded from 5.30 for participants who indicated "yes" on 5.29 Project Mind Codebook: BaseT_Lostincomeamount

Psychosocial circumstances (social support and social capital)		
Relationship status	Categorical – nominal	Coded from 2.8 of the baseline assessment: (2) Single: Coded from options of the baseline assessment: Widow/widower (2.8.3) and Never married (single) (2.8.5) (0) Divorced: Coded from options of the baseline assessment: Divorced or separated (2.8.4) (1) Significant other: Coded from options of the baseline assessment: Married (2.8.1) and Living with partner (2.8.2) Option: "other" will be excluded from the analysis Project Mind Codebook: BaseT_Relationship_Status_Cat
Social support	Numerical – continuous	Mean (Standard Deviation) Coded from options 10.2 – 10.20 of the baseline assessment (higher score indicating more social support) Project Mind Codebook: BaseT_MOSSupport_Compsite transformed
Social problem-solving	Numerical – continuous	Mean (Standard Deviation) Coded from options 10.48 – 10.57 of the baseline assessment. The variable will be categorized according to the social problem-solving styles (Sorsdahl et al., 2017). Higher scores in the Negative problem orientation, Impulsivity-carelessness style and Avoidant style reflect a more maladaptive approach to problem solving (Hawkins et al., 2009). Higher scores on the Positive problem orientation and Rational problem solving indicate more adaptive problem solving (Hawkins et al., 2009). Positive problem orientation: ● (10.25) When my first efforts to solve a problem fail, I give up quickly because finding a solution is too difficult ● (10.26) Sometimes even difficult problems can have a way of moving my life forward in positive ways ● (10.30) Whenever I have a problem, I believe that it can be solved ● (10.34) When problems occur in my life, I like to deal with them as soon as possible ● (10.36) When I am faced with a difficult problem, I believe that I will be able to solve it on my own if I try hard enough Project Mind Codebook: BaseT_SPSI_PPO Rational problem solving: ● (10.33) When I have a decision to make, I take the time to try to predict the positive and negative consequences of each possible option before I act ● (10.37) When I have a problem to solve, one of the first things I do is get as many facts about the problem as possible ● (10.40) Before I try to solve a problem, I set a specific goal so that I know exactly what I want to accomplish ● (10.42) After carrying out a solution to a problem, I try to evaluate as carefully as possible how much the situation has changed for the better ● (10.44) When I am trying to solve a problem, I think of as many options as possible until I cannot come up with any more ideas Project Mind Codebook: BaseT_SPSI_RS Avoidant style: ● (10.27) If I avoid problems, they will generally go away on their own

		● (10.31) I try to do anything I can in order to avoid problems in my life ● (10.38) When a problem happens in my life, I put off trying to solve it for as long as possible ● (10.39) I spend more time avoiding my problems than solving them ● (10.43) I put of solving problems until it is too late to do anything about them Project Mind Codebook: BaseT_ SPSI_AS Negative problem orientation ● (10.22) I feel afraid when I have an important problem to solve ● (10.24) I get nervous and unsure of myself when I have to make an important decision ● (10.28) When I can't solve a problem, I get very frustrated ● (10.29) If I am faced with a difficult problem, I probably will not be able to solve it on my own no matter how hard I try ● (10.31) Difficult problems make me very upset Project Mind Codebook: BaseT_SPSI_NPO Impulsivity-carelessness style ● (10.23) When making decisions, I do not think carefully about my many options ● (10.35) When I am trying to solve a problem I go with the first good idea that comes to mind ● (10.41) When I have a decision to make, I do not take the time to consider the pros and cons of each option ● (10.45) When making decisions, I go with my "gut feeling" without thinking too much about what can happen ● (10.46) I am too impulsive when it comes to making decisions Project Mind Codebook: BaseT_SPSI_ICS

Appendix C: Study budget

Category	Item	Cost
Stationary:	Paper	R100
Printing:	Ink cartridges	R500
	Final report	R400
Incidental:		R100
		Total = R1100

Appendix D: Study logistics

Activity	Feb 2023	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan 2024
Finalise Protocol (PART A)	x	x	x									
Obtain Ethics Approval			x	x	x							
Full Literature review (PART B)			x	x	x							
Analyse data (PART C and D)						x	x	x				
Write up (PART C and D)							x	x	x			
Draft Dissertation / Journal manuscript (PART C)									x	x		
Finalise dissertation (PART C) and policy brief (PART E)										x	x	
Submission												x

Appendix E: Human Research Ethics Committee approval

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

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

10 August 2023

HREC REF: 559/2023

Dr A Obse
Health Economics Unit
FHS
Email: g.amarech@gmail.com
Student: tntsus001@myuct.ac.za

Dear Dr Obse

PROJECT TITLE: SOCIAL DETERMINANTS OF COMORBID DEPRESSION AMONG PATIENTS LIVING WITH DIABETES AND HIV AT PRIMARY HEALTHCARE SETTINGS IN WESTERN CAPE PROVINCE OF SOUTH AFRICA
(MASTER'S CANDIDATE - MS SUSANET TINTINGER)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

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 August 2024.

Please submit a progress form, using the standardised Annual Report Form (FHS016) 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)

The HREC acknowledge that the student: Ms Susanet Tintinger will also be involved in this study.

Please quote HREC REF 559/2023 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.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

HREC/ref 559.2023

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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), 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 Federal Regulation Part 50, 56 and 312.

HREC/ref 559.2023

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)			
☑ Approved	☑ Type of review: Expedited	☐ Full committee	
This serves as notification that all changes and documentation described below are approved.			
Signature HREC Chairperson / Designee		Date	18/12/2023

Note: All **Major** amendments must include a **Cover Letter** and a local **PI Synopsis** justifying the changes for the amendment. Please note that incomplete amendment submissions will not be reviewed.

Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za with subject line: FHS006 + (HREC Reference number).

The latest forms are found on our website.

http://www.health.uct.ac.za/fhs/research/humanethics/forms

Please also clarify your plan for research-related activities during COVID-19 lockdown:

Comments from the HREC to the Principal Investigator:
Note: The approval of this protocol amendment does not grant annual approval. Please complete the FHS016 / FHS017 form for annual approval at least one month before study expiration.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	12 December 2023		
HREC REF Number	HREC REF: 559/2023		
Protocol Title	Social determinants of comorbid depression among patients living with diabetes and HIV at primary healthcare settings in Western Cape Province of South Africa		
Protocol Number (if applicable)			
Principal Investigator	Dr Amarech Obse		
Department / Office Internal Mail Address	Health Economics Unit ag.obse@uct.ac.za g.amarech@gmail.com		
1.1 Is this a major or a minor amendment? (see FHS006hlp) Major (tick box) Minor (tick box)		☐ Major	☑ Minor

1.2 Does this protocol receive US Federal funding?	☐ Yes	☑ No
1.3 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval? **Note:** Any protocol amendments for **Full Committee Review** MUST be submitted on the monthly HREC submission dates. (Please email an electronic copy to hrec-enquiries@uct.ac.za)	☐ Yes	☑ No
1.4 Did the initial study require UCT No-Fault Insurance	☐ Yes	☑ No

2. List of Proposed Amendments with Revised Version Numbers and Dates

Please itemise on the page below, all amendments with revised version numbers and dates, which need approval.
This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.

Included in this submission is:

1. The original protocol (version 1) dated 24 April 2023 submitted to HREC and for which ethical approval was received (HREC REF: 559/2023). Amendments are indicated on this document with track changes.
2. A "clean copy" of the protocol (version 2) with the proposed amendments dated 12 December 2023.

3. Protocol status (tick ✓)

☐	Open to enrolment
☐	No participants have been enrolled
	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☑	Research-related activities are complete, data analysis only

4. Proposed changes will affect: (tick ✓ all the categories that apply)

Protocol	
☐	Study objectives, design (including investigator's brochure, clinical activities, study length)
☐	Study instruments, questionnaires, interview schedules
☐	Sample size
☐	Recruitment methods

☐	Eligibility criteria (inclusion and exclusion criteria)
☐	Drug/device (composition, amount, schedule, route of administration, combination with other drugs/devices, safety information)
☑	Data collection/ analysis
☐	Principal Investigator. (Please attach revised conflict of interest and PI declaration statements. Refer: sections 7 and 8.4 in the New Protocol Application Form FHS013)
☐	Consent form and information sheet
☐	Recruitment materials (e.g. advertisements)
☐	Administrative (e.g. change in sponsor's name, change in contact information)
☐	Other. Please specify:

**Note: Amendment changes involving study length, sample size, additional sites and eligibility criteria (i.e. inclusion of minors and /or pregnant woman) need to be declared to the Insurance office. Please liaise via fhs.sponsorship@uct.ac.za regarding the required documentation and information to be submitted to obtain an updated UCT No-fault Insurance Certificate- it should be included herewith*

4.1 In your opinion, will there be any **increase** in risk, discomfort or inconvenience to participants?	☐ Yes	☑ No
If yes, please provide a detailed justification/explanation:		

4.2 What follow-up action do you propose for participants who are already enrolled in the study?	
☐	Inform current participants as soon as possible
☐	Re-consent current participants with revised consent/assent forms (append)
☑	No action required
☐	Other. Please describe:

5. Detailed description of the change(s)

Please attach, for each amendment, a summary of all changes which clearly indicates:

i. Old wording (e.g. ~~strikethrough~~ text, CHANGED FROM and CHANGED TO)

ii. New wording (e.g. *italicized*, **bold**, tracked)

iii. Detailed rationale/ justification/ explanation for each change

6. Ethics Review for Amendment Levy – cost including vat

Amendment Review Costs including VAT

Please tick amount to be billed:

Submission Type	*Description*	*New fee (Vat Incl.)*	*tick ✓*
Research funded solely from UCT departmental/ divisional/group budget	Major/ Minor Amendments	**R0,00**	☑
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Major/ Minor Amendments	R0,00	☐
Protocol amendment - Major (FHS006 Form)	Clinical Trial & International Grant Funded Research - Any changes to the protocol that requires Full Committee review	**R8 000.00**	☐
Protocol amendment - Major (FHS006 Form)	Clinical Trial & International Grant Funded Research - Any change to the protocol that requires Expedited review that does not require Full Committee Review	**R5 000,00**	☐
Protocol amendment - Minor (FHS006 Form)	Clinical Trial & International Grant Funded Research - Minor amendments, administrative changes that do not affect study design e.g. changes to informed consent form, changes in study staff, etc.	**R2 250,00**	☐
Protocol amendment - Major (FHS006 Form)	National grant funded research - Any change to the protocol that requires Full Committee review	**R7 000,00**	☐
Protocol amendment - Major (FHS006 Form)	National grant funded research - Any change to the protocol that requires Expedited review that does not require Full Committee review	**R2 500,00**	☐
Protocol amendment - Minor (FHS006 Form)	National grant funded research - Minor amendments, administrative changes that do not affect study design e.g. changes to informed consent form, changes in study staff, etc.	**R1 000,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	
Vat Number:	
Contact person:	
Telephone number:	
Email Address:	

2. Internal Journal Billing:

Fund Number:	

Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

7. Amendment Submission checklist (tick ✓)

7.1 Please tick that all the documents are attached before submitting to the HREC. NB: Incomplete submissions will not be processed	
☑	Latest FHS006 form completed with all sections completed as per our website
☑	Cover Letter
☑	PI Justification/ Summary for the reasons for the amendment
☑	Protocol - Track changes & Clean Copy (where necessary)
☐	Informed Consent Forms (ICF), if applicable (Any changes made to ICF tracked & clean copy)
☐	Any other additional documentation in support of amendment
☐	Updated no fault insurance certificate (if applicable)

Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za with subject line: FHS006 + (HREC Reference number). The latest forms are found on our website.

8. Signature

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.

Signature of PI	Dr Amarech Obse	Date	12/12/2023

Appendix F: BMC Submission guidelines

BMC Psychiatry Available from: https://bmcpsychiatry.biomedcentral.com/submission-guidelines

Research articles should report on original primary research or new experimental or computational methods, tests or procedures. Manuscripts reporting results of a clinical trial must conform to CONSORT 2010 guidelines. Authors of randomized controlled trials should submit a completed CONSORT checklist alongside their manuscript, available at www.consort-statement.org. Research articles may also report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research and bibliometric analyses will not be considered. Studies reporting descriptive results from a single institution or region will only be considered if analogous data have not been previously published in a peer reviewed journal and the conclusions provide distinct insights that are of relevance to a regional or international audience.

BMC Psychiatry strongly supports open research, including transparency and openness in reporting. Further details of our Data availability policy can be found on the journal's About page.

BMC Psychiatry strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature's data repository guidance. Where a widely established research community expectation for data archiving in public repositories exists, submission to a community-endorsed, public repository is mandatory. A list of data where deposition is required, with the appropriate repositories, can be found on the Editorial Policies Page.

Cropped gels and blots can be included in the main text if it improves the clarity and conciseness of the presentation. In such cases, the cropping of the blot must be clearly evident and must be mentioned in the figure legend. Corresponding uncropped full-length gels and blot must be included in the supplementary files. These uncropped images should indicate where they were cropped, be labelled as in the main text and placed in a single supplementary figure. The manuscript's figure legends should state that 'Full-length blots/gels are presented in Supplementary Figure X'. Further information can be found under 'Digital image integrity' which are detailed on our Standards of Reporting page.

Professionally produced Visual Abstracts

BMC Psychiatry will consider visual abstracts. As an author submitting to the journal, you may wish to make use of services provided at Springer Nature for high quality and affordable visual abstracts where you are entitled to a 20% discount. Click here to find out more about the service, and your discount will be automatically be applied when using this link.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
  - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
  - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors
  - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below
  - Large Language Models (LLMs), such as ChatGPT, do not currently satisfy our authorship criteria. Notably an attribution of authorship carries with it accountability for the work, which cannot be effectively applied to LLMs. Use of

an LLM should be properly documented in the Methods section (and if a Methods section is not available, in a suitable alternative part) of the manuscript.

- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

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- Consent for publication
- Availability of data and materials
- Competing interests
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- Authors' contributions
- Acknowledgements
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Acknowledgements

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