2020

Comorbidity of serious mental illness and type 2 diabetes: do neighbourhoods matter?

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Comorbidity of serious mental illness and type 2 diabetes: do neighbourhoods matter?

A thesis submitted in fulfilment of the

requirements for the award of

Doctor of Philosophy

from the

University of Wollongong

by

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School of Medicine,

Faculty of Science, Medicine and Health

2020

CERTIFICATION

I, Ramya Walsan, declare that this thesis, submitted in fulfillment of the requirements for the award of Doctor of Philosophy, in the Faculty of Science, Medicine and Health, University of Wollongong is wholly my own work and that any work adopted from other sources is duly acknowledged or referenced. This document has not been submitted for qualifications at any other academic institutions.

Signed: ……..

(Ramya Walsan)

STATEMENT OF CONTRIBUTION

This statement verifies that the greater part of the work in the below named manuscripts is attributed to the candidate, Ramya Walsan. She contributed to the study conception and design, undertook literature review and data analysis, prepared the first and final draft of each manuscript for submission to the relevant journals. Supervisors contributed to the study design, critically reviewed the manuscripts, and provided editorial suggestions.

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Dr Darren John Mayne (Co-supervisor)

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DEDICATION

This thesis is dedicated to my parents Dr Bhargavi and Adv K.R Walsan, whose boundless love and encouragement have made this work possible. Their confidence in me has been steadfast making it impossible for me to lose confidence in myself. May this work honour their dedication in supporting me throughout my life.

ACKNOWLEDGEMENTS

I am immensely grateful for my primary supervisor Prof Andrew Bonney. Over the past three years he has graciously guided me through the ups and downs of this candidature with patience, kindness and selflessness. Andrew's expertise, wisdom and support have been the critical pieces to my success in this doctoral program. This thesis owes its completion to his wonderful supervision.

I am thankful for the support of Prof Nagesh Pai, one of my co-supervisors. Nagesh has provided invaluable advice and counsel particularly in the mental illness component of this research. His guidance and support have been instrumental in encouraging me to pursue this PhD. I also gratefully acknowledge the expertise, support and encouragement provided by my co-supervisor Dr Xiaoqi Feng. Her constructive feedback and comments have been invaluable in developing this body of work. I am also grateful to her for offering me a research assistant opportunity in her lab allowing me to work on interesting projects. My sincerest gratitude also goes to my other co-supervisor Dr Darren Mayne for his generous advice and steadfast support from the outset. The opportunity to draw on his extraordinary breadth of knowledge and expertise, especially in the field of spatial and statistical analysis was highly remarkable.

I owe a debt of gratitude to Illawarra Shoalhaven Local Health District and University of Wollongong for providing me with a PhD scholarship to pursue this PhD. I would also like to acknowledge the Faculty of Science, Medicine and Health, University of Wollongong for providing me with a travel grant to present my study findings.

I would like to thank my fellow PhD student Ms Renin Toms for her friendship, support and for sharing many laughs together. Assistance provided by her for my systematic literature review is also greatly appreciated.

I am deeply indebted to my parents, my sister and my friends for their loving support throughout the course of this PhD. A very special thanks goes to my beautiful daughters Aiswarya and Anjali for their support and encouragement and to my fur baby Coco for his company and unconditional love. The biggest and the final thanks goes to my loving husband Biju, who stood by my side throughout this journey. No words can capture my gratitude for his encouragement, patience and unwavering belief in me.

ACKNOWLEDGEMENT OF DATA PROVIDER

I am thankful to Illawarra Health Information Platform (IHIP), a research partnership established between the Illawarra Shoalhaven Local health District (ISLHD) and the University of Wollongong for providing the data used in this study. https://ahsri.uow.edu.au/chrisp/ihip-data/index.html.

I am also grateful to Southern IML Pathology and staff for providing the General diabetes (Gen-DM) and Body Mass Index (BMI) data from the SIMLR (Southern IML Research) cohort study for use in this research. Southern IML pathology are the owners of Gen-DM and BMI data contained within this thesis and Illawarra Health and Medical Research Institute (IHMRI) is the custodian facilitating access to this data. https://www.ihmri.org.au/research-projects/simlr-cohort-study/

PUBLICATIONS CONSTITUTING THIS THESIS

PUBLISHED ARTICLES

Walsan, R., Bonney, A., Mayne, D.J., Pai, N., Feng, X., & Toms, R., 2018, 'Serious Mental Illness, Neighbourhood Disadvantage, and Type 2 Diabetes Risk: A Systematic Review of the Literature'**,** Journal of Primary Care & Community Health, Vol 9, p 1-7. **(Chapter 2).**

Walsan, R., Mayne, D.J., Pai, N., Feng, X., & Bonney, A., 2019, 'Exploring the geography of serious mental illness and type 2 diabetes comorbidity in Illawarra—Shoalhaven, Australia (2010 -2017), PLOS ONE, 14 (12), p 1-13.**(Chapter 3).**

Walsan, R., Mayne, D.J., Feng, X., Pai, N., & Bonney, A., 2019, 'Examining the Association between Neighbourhood Socioeconomic Disadvantage and Type 2 Diabetes Comorbidity in Serious Mental Illness', International Journal of Environmental Research and Public Health, 16 (20). **(Chapter 4).**

Walsan, R., Feng, X., Mayne, D.J., Pai, N., & Bonney, A., 2020, 'Neighbourhood environment and type 2 diabetes comorbidity in serious mental illness', Journal of Primary Care and Community Health, 11, p 2150132720924989. **(Chapter 5)**.

OTHER PUBLICATIONS

Walsan, R., Bonney, A., Mayne, D.J., Feng, X., Vella, S.L., Pai, N., 2020, 'Neighbourhoods and physical health comorbidity in individuals with serious mental illness'. Schizophrenia research, 222, p 509-510.

PRESENTATIONS ARISING FROM THIS THESIS

CONFERENCE PRESENTATIONS

Walsan, R., Bonney, A., Mayne, D.J., Pai, N., Feng, X., & Toms, R., 2018, 'Neighbourhood disadvantage and type 2 diabetes comorbidity in serious mental illness: A systematic review of literature', E- poster presented at The Mental Health Services Conference 2018, Adelaide, Australia.

Walsan, R., Bonney, A., Mayne, D.J., Pai, N., & Feng, X., 2019, 'Spatial analysis of serious mental illness and type 2 diabetes comorbidity: Is there evidence of clustering?' , Oral presentation at 5th International Conference on Public Health, Kuala Lumpur, Malaysia

Walsan, R., Bonney, A., Mayne, D.J., Pai, N., & Feng, X., 2019, 'Geographic inequalities in the distribution of serious mental illness - type 2 diabetes comorbidity', Oral presentation at 18th International Medical Geography Symposium, Queenstown, New Zealand.

Walsan, R., Mayne, D.J., Feng, X., Pai, N., & Bonney, A., 2020, 'Neighbourhoods matter too: Association between neighbourhood socioeconomic disadvantage and type 2 Diabetes Comorbidity in serious Mental Illness', e-oral presentation at 2020 Congress of International Schizophrenia Research Society, Florence, Italy.

OTHER PRESENTATIONS

Serious mental illness and type 2 diabetes comorbidity: Do neighbourhoods' matter? – Presented at Wollongong Hospital Grand rounds, May 2016**.**

Neighbourhoods and type 2 diabetes comorbidity in serious mental illness – Presented at Illawarra Shoalhaven Local Health District Research Dinner, June 2016

Type 2 diabetes in people with serious mental illness: The role of neighbourhoods – Presented at Illawarra and Southern Practice Research Network Conference, August 2016

Comorbidity of serious mental illness and type 2 diabetes: do neighbourhoods' matter? - Presented research proposal at the Faculty of Science Medicine and Health HDR proposal seminar, July 2017.

THESIS ABSTRACT

Background: Serious mental illness (SMI) refers to mental disorders that are severe in degree, persistent and produce considerable functional impairment, and include conditions such as schizophrenia, bipolar disorder or major depression. Type 2 diabetes (T2D) is 2 - 4 times more prevalent in people with SMI and contributes significantly to the increased morbidity and mortality experienced by this group. Even though antipsychotic medication is recognised as a major risk factor for T2D in individuals with SMI, there are likely additional biopsychosocial mechanisms involved that may independently contribute to SMI-T2D comorbidity. One possible correlate that has not been adequately investigated in this context is the neighbourhood environment. There is strong evidence that people with SMI are more likely to live in socioeconomically disadvantaged neighbourhoods with poorer resources and infrastructure. These neighbourhood influences have been associated with traditional risk factors of diabetes such as inactive lifestyle, unhealthy food choices and obesity. Despite the plausibility, little evidence is available on the associations of neighbourhood contextual factors with SMI-T2D comorbidity.

Aims: The principal aims of this thesis were threefold. First, to describe the geography of SMI-T2D comorbidity in the Illawarra-Shoalhaven region of NSW, Australia. Second, to explore the cross-sectional association between neighbourhood-level socioeconomic disadvantage and SMI-T2D comorbidity. Third, to identify the specific features of disadvantaged neighbourhood environments that are associated with SMI-T2D comorbidity.

Methods: The analysis considered 3816 individuals with a diagnosis of SMI living in the Illawarra-Shoalhaven regions of NSW, Australia, between 2010 and 2017. A combination

of spatial and multilevel modelling approaches was used to assess the association between neighbourhoods and SMI-T2D comorbidity.

Results: Significant geographic variation was observed in the distribution of SMI-T2D comorbidity in the Illawarra-Shoalhaven. High risk clusters were mainly observed in the urban areas surrounding the major metropolitan centre. Individuals with SMI residing in the most disadvantaged neighbourhoods had 3.2 (95% CI 1.42 - 7.20) times higher odds of having SMI-T2D comorbidity compared to residents in the least disadvantaged neighbourhoods, after controlling for individual level factors. A significant positive association was also observed between area level crime rates and SMI-T2D comorbidity independent of individual-level characteristics and neighbourhood-level socioeconomic disadvantage (OR 2.78 (1.02 - 7.57). No evidence of association was found between neighbourhood resources such as health care access, fast food availability and green spaces and SMI-T2D cooccurrence. Among the individual level variables, increasing age was identified as a significant correlate of comorbidity.

Conclusions: These findings highlight the importance of considering the role of neighbourhood environments along with individual level risk factors in influencing T2D risk in people with SMI. The findings also suggest the potential for geographically targeted initiatives designed to enhance prevention and management of SMI-T2D comorbidity in socioeconomically disadvantaged and high crime neighbourhoods. Future research should incorporate longitudinal study designs, data from different geographic locations, and mediation analyses to further elucidate the mechanisms linking neighbourhoods and T2D comorbidity in SMI.

LIST OF KEY ACRONYMS

SMI	Serious Mental illness
GIS	Geographic Information Systems
ASGS	Australian Statistical Geography Standard
ABS	Australian Bureau of Statistics
IRSD	Index of Relative Socioeconomic Disadvantage
SEIFA	Socioeconomic Indexes for Area
UOW	University of Wollongong
ISLHD	Illawarra Shoalhaven Local Health District
SIMLR	Southern IML Research
BMI	Body Mass Index
LISA	Local Indicators of Spatial Association
FDR	False Discovery Rate
DAG	Directed Acrylic Graph
IHIP	Illawarra Health Information Platform
APDC	Admitted Patient Data Collection
ICD10-AM	International Classification of Diseases-Australian Modification
HbA1C	Haemoglobin A1c
BOSCAR	NSW Bureau of Crime Statistics and Research
NHSD	National Health Service Directory

AURIN	Australian Urban Research Infrastructure Network
2SFCA	Two Step Floating Catchment Area
OSM	Open Street Map
SDH	Social Determinants of Health
SSC	State Suburb Codes
MAUP	Modifiable Areal Unit Problem

TABLE OF CONTENTS

List of tables

List of figures

CHAPTER 1

Introduction

Overview

Type 2 diabetes (T2D) comorbidity is highly prevalent in serious mental illness (SMI) and is associated with significant personal and public health burden [1-6]. While many studies investigating this comorbid association have considered individual level risk factors, this thesis examines the neighbourhood correlates of SMI-T2D comorbidity. Impetus for this study was provided by the following six interweaving streams of evidence or health care imperatives:

i. A greater risk of T2D in individuals with SMI leading to morbidity and premature mortality in these populations [1-4].

ii. An increased focus by health care systems and policy makers on addressing these inequalities and the large mortality gap experienced by individuals with SMI [7].

iii. The plausibility of an association between neighbourhoods and SMI-T2D comorbidity as individuals with severe mental illness are highly likely to live in disadvantaged neighbourhoods due to their lower socioeconomic status [8, 9]. Poor quality environment in these neighbourhoods may aggravate the experiences of psychosocial stress or promote engagement in adverse health behaviours such as unhealthy eating, physical inactivity and obesity; all of which contribute to T2D risk [8, 10, 11].

iv. The effectiveness of population-based prevention strategies complementary to individual based approaches in reducing the chronic disease burden as they shift the risk distribution of the entire populations in a favourable direction [12].

v. An enhanced interest in recent years in addressing comorbid conditions concurrently along with the social and environmental factors in which they are found, as illustrated by the 'Syndemics' approach [13].

vi. The need to develop evidence based prevention and intervention programmes to reduce the public health burden imposed by the SMI-T2D comorbidity [1].

This first chapter of the thesis describes the background and the rationale upon which the thesis is based. This chapter commences by describing the comorbid relationship between SMI and T2D and is followed by supporting evidence regarding neighbourhoods and health. The association between neighbourhoods and SMI-T2D comorbidity is then reviewed and gaps in the available literature are identified. Finally, the aims of this thesis are listed, and an overview of the thesis structure is provided.

Background

Mental disorders such as schizophrenia, bipolar disorder or major depression, that are severe in degree and produce significant functional impairment, are referred to as serious mental illness [14]. Research literature has long established the association between serious mental illness and type 2 diabetes [15]. In 1879, Sir Henry Maudsley in "The pathology of mind" defined diabetes as a "disease which often shows itself in families in which insanity prevails" [16]. Modern research reports higher T2D prevalence rates of approximately 15% in populations with serious mental illnesses, which represents a two to four-fold increase in risk compared with the general population [1, 2, 4]. Both SMI and T2D impart significant individual and public health burden when present individually and are the two leading causes of disability and ill-health worldwide [17]. The comorbid association compounds this burden by worsening the outcomes for each of these conditions [18]. In those with SMI, a comorbid T2D diagnosis not only confers a higher cardiovascular risk and a reduced life expectancy of about 15-30 years, but is also

associated with: increased microvascular and macrovascular complications affecting several organs; increased hospitalisations; greater number of emergency department visits; non-adherence to treatments; higher healthcare utilisation costs; and decreased quality of life [2-6]. Studies have reported that people with comorbid schizophrenia and type 2 diabetes have worse cognitive impairment than schizophrenia without diabetes or diabetes alone, which can significantly impede their rehabilitation and can lead to poorer clinical and functional outcomes [19, 20].

Prevalence of type 2 diabetes in individuals with serious mental illness.

Several studies have estimated varying T2D prevalence in individuals with SMI ranging from 1.3 to 68% , with a median of 13 % [1, 2, 4, 21, 22]. The variations in study design, heterogeneity of study populations, inclusion of different stages of illness and differences in sample sizes are likely to have contributed to this wide variation in the prevalence estimates. For example, the Australian study which reported the highest estimate of 68 %, investigated psychotic patients in a psychiatric rehabilitation program and had many people with chronic psychotic illness for a longer period and on polypharmacy involving more than one antipsychotics [22]. Another Australian study reported double the prevalence of metabolic syndrome in patients with SMI compared to the general population [23] . The authors also reported no significant change in prevalence depending on age, sex and Aboriginal status.

Risk factors for diabetes in people with SMI

The association between SMI and diabetes is highly complex and multifactorial. People with psychotic disorders are more prone to many of the traditional risk factors of diabetes such as obesity, lower physical activity and unhealthy diet, making them a higher risk population [24]. Obesity is a prominent observation in people with serious mental illness with an estimated relative risk ratio of 1.5 to 3.5 [4]. Higher body mass index (BMI) and

waist circumference than the general population is observed in individuals with SMI as young as 25 years; and even at their first presentation with SMI. These findings are partly explained by the adverse health behaviours such as poor diet and lower physical activity consistently reported in individuals with SMI [4, 25, 26]. For example, a study in Australia, which examined fruit and vegetable intake in people with psychosis, reported that 74% of the patients did not eat adequate amounts of fruits and vegetables [25]. The fruit and vegetable intake in this population were approximately 50 - 55 % lower than the Australian general population. Higher consumption of fast food than the general population was observed in a British study examining the dietary pattern of patients with schizophrenia living in community homes [26]. More than a third of these patients reported consuming fast food at least three times a week, often in addition to their regular meals. Similarly, inadequate physical activity or sedentary lifestyle among people with SMI is widely documented [4, 27]. Gallety et al. (2012), studied physical activity among people with psychosis in Australia and found that 96.7 % of patients had low to very low levels of physical activity [27].

First and second-generation antipsychotics used in the treatment of SMI are also implicated in the excess risk of T2D in individuals with SMI. These are thought to induce diabetes both directly by promoting insulin resistance and indirectly by causing weight gain due to their ability to increase appetite [2]. However, there are studies reporting higher diabetic risk in patients with SMI even before antipsychotic treatments [28] as well as studies not showing any significant association between the antipsychotic medications and SMI-T2D comorbidity [29].

Psychotic disorders themselves may act as risk factors for type 2 diabetes as there are claims regarding their common genetic links [29, 30]. Studies have also shown that the risk increases with the duration of the disease [31]. Age is also considered a significant

risk factor in the development of type 2 diabetes in individuals with SMI, and this might be associated with increased disease duration [32]. Age at first psychiatric admission is also reported to be a significant predictor for T2D risk [18]. Additionally, the cognitive impairment associated with psychiatric disorders can lead to reduced adherence and adoption of health promoting practices resulting in adverse diabetic outcomes [33].

More recently, chronic stress has been recognised as an important risk factor in the development of diabetes. Individuals with SMI experience physical and psychological stress which is thought to cause altered immune function and chronic inflammation resulting in higher concentrations of inflammatory cytokines which can decrease insulin function [34]. A literature review by Manu et al. (2014), found a robust association between first episode and relapsed schizophrenia and pro inflammatory cytokines [35]. Stress is also thought to increase the stress-hormone cortisol by acting on hypothalamus-pituitary-adrenal axis [2]. Increased concentrations of stress hormone and enlarged pituitary glands have also been observed in patients with psychotic disorders [36] .

Syndemic framework for SMI-T2D comorbidity

Syndemics refers to the presence of two or more synergistic diseases that adversely interact with each other and are exacerbated by the social, environmental and economic situations in which they are found [37]. The Syndemic framework offers a novel approach for the investigation of disease clustering and has gained increasing recognition in recent years [38]. Adverse socioecological conditions such as poverty, discrimination, adverse neighbourhood environments, unstable housing are theorised to drive the development of Syndemics, which in turn leads to vulnerability and risky health behaviours leading to disease clustering [13]. A Syndemic framework is comprised of three key phenomena: (i) two or more diseases that cluster or are comorbid within a given population; (ii) contextual and social factors promoting disease clustering; and (iii) bidirectionality and/or

interaction between these diseases. Bidirectionality and synergetic association between SMI and T2D is widely documented in research literature [18], suggesting the existence of a SMI-T2D Syndemics. The conceptualisation of SMI and T2D as a Syndemic may be useful in identifying the correlates of SMI-T2D comorbidity that could become the targets for future intervention.

Neighbourhoods and health

Neighbourhoods are emerging as an important context in public health epidemiology, representing physical and social attributes responsible for resident health [39]. This explosion of interest reflects both the theoretical discussions concerning social determinants of health [40] and the growing recognition that individual characteristics cannot exclusively capture all the causes of ill health [41]. Studies have established that people who live in disadvantaged environments or neighbourhoods have poorer mental and physical health outcomes than people living in non-disadvantaged areas [41, 42]. This phenomenon is commonly referred to as the social gradient of health [41]. There is an increased focus in recent years on developing evidence-based interventions, health care policies [43] and even designing healthy life spaces [44], all of which warrant a better understanding of the health-geography association. In addition, the availability and popularity of newer methodological approaches such as multi-level analysis, Geographic Information Systems (GIS) [45], spatial analysis [46, 47] and most recently Directed Acyclic Graphs (DAG) [48, 49] have all stimulated empirical research in this field.

Neighbourhood effects on health are usually explained in terms of contextual or compositional effects [50]. The compositional effect posits that neighbourhood effects are the function of the individual characteristics of people living in the area [41]. For example, it is widely recognised that less wealthy people have increased mortality compared with their wealthier counterparts [51]. So, it is rational to expect that areas with

higher concentration of disadvantaged population will have higher mortality rates. Contextual effect argues that area properties contribute to the differential in health across neighbourhoods [41]. The following thesis is focussed on contextual effects. Nonetheless, it is acknowledged that both these neighbourhood effects are highly interconnected and should not be considered as distinct influences.

Neighbourhoods affect the health of residents mostly by limiting the choices and resources available for use [52]. Moreover, a neighbourhood environment provides cues that support social norms defining individuals' healthy behaviours, which can be compromised in a disadvantaged neighbourhood [53]. Neighbourhood factors affecting health can be physical or social [54]. Physical environment refers to the physical features of the environment such as our homes, natural features, parks/recreation areas, land use, transport systems, healthcare resources and even availability of fresh food stores [55]. Increasing attention has been placed on health behaviours affected by physical environments that are created and modified by people, which are commonly referred to as the 'built environment' [55]. Social environmental factors refer to the immediate social surroundings of an individual such as cultures, institutions, workplaces and even policies within which they live and interact [56] . This can include social cohesion, social support, social networks, neighbourhood violence and disorder and may contribute to health through stress and adverse health behaviours [41]. Previous research has shown that people with more social connections and social ties have better overall health and reduced mortality [56, 57].

One of the main challenges associated with area level research in health is in regard to the conceptualisation and measurement of neighbourhoods [58]. Neighbourhoods or an individual's immediate residential environment is defined in public health research using a wide variety of definitions and geographic scales, making it difficult to combine and

compare evidence across studies [59, 60]. Administrative boundaries are one of the widely used proxies for neighbourhoods/communities in many studies [61]. However, they are subjected to the modifiable area unit problem (MAUP), where results can vary depending on the number and scale of the area used to define a neighbourhood [62]. Furthermore, the appropriate geographic scales are likely to vary for different health outcomes, processes, populations, and the neighbourhood level measures investigated [61]. For example, administratively defined boundaries may be appropriate for neighbourhood processes that involve policies; neighbourhoods defined based on people's perception may be more appropriate when characteristics such as social cohesion/support are investigated and a geographically defined neighbourhoods such as circular buffers/road network buffers may be relevant when physical or anthropogenic neighbourhood environments are studied [63]. Identification of appropriate neighbourhoods should be an important consideration in the identification of true contextual effects.

Another common criticism faced by neighbourhood research is that the neighbourhood effects are subjected to confounding by individual level factors [41]. For example, it is commonly proposed that well-maintained public places in neighbourhoods are associated with increased social mixing and improved mental wellbeing. However, it is possible that the decision on having a common area was in response to the preference for social mixing among the local residents. In this case, preference for social mixing is an unobserved individual variable that is related to the location of common areas and mental wellbeing in the neighbourhood. Another commonly cited example of this is the problem of self-selection [41]. Neighbourhood self-selection arises when individuals are sorted into neighbourhoods based on their lifestyle preferences and other sociodemographic characteristics and these characteristics may be related to health outcomes [64]. Various

strategies are proposed to control for individual confounding including longitudinal study designs, comprehensively identifying, and controlling for unobserved predictors (using multilevel modelling), propensity score matching [65] and instrumental variable estimation [66]. However, it should be noted that the inferences from neighbourhood studies will be limited if important individual level variables are omitted or are subjected to systematic measurement errors [63].

Neighbourhoods and serious mental illness

Researchers have long commented on the association between adverse neighbourhood characteristics and mental wellbeing. In 1939, Faris and Dunham [67] argued that the rates of schizophrenia and substance abuse were highest among the socially deprived and disorganised inner-city neighbourhoods of Chicago. Several studies have followed, particularly in the last 25 years, establishing a persistent positive relationship between the characteristics of the place of residence and mental illness [68-70].

An early study in Nottingham (1998), a city in the UK, identified a higher rate of schizophrenia in the most deprived neighbourhoods [68]. Another investigation by Kirkbride et al. (2007) [64] found the rates of affective psychotic disorders to be highest in the areas with the highest social deprivation. In addition, the study reported that neighbourhood level risk factors accounted for 23% of the variance in the incidence of psychotic disorders [71]. Many of the relevant individual level variables such as individual socioeconomic status and family history were not accounted for in this analysis. These unobserved variables could have been spatially structured and may have contributed to the high estimate of neighbourhood level effect in the above study.

Research on neighbourhood contextual factors affecting mental health has covered a broad range of features such as neighbourhood socioeconomic deprivation [72, 73],

availability and accessibility of health services [74], built environment [75], presence of tobacco and alcohol vendors [76], social capital [77] and social disorder [78]. To date, there have been relatively few studies exploring mental health and neighbourhoods in Australia [49, 79]. In Melbourne, O'Donoghue et al. (2015) studied the level of social deprivation in the area of residence at the time of initial contact with the health service on risk of progressing to full threshold psychotic disorder and did not find any significant relationship [79]. Another study reported an increased use of the emergency department among people with SMI for mental health reasons with an increase in socioeconomic disadvantage [80].

A prominent area of enquiry in geographic research in SMI is whether the higher observed incidence in the most deprived areas is due to 'social causation' and/or 'social drift' processes [67, 81]. The social causation hypothesis proposes that factors associated with disadvantage such as poverty, lack of social support, crime rates, reduced health care access in disadvantaged neighbourhoods over time increase the risks of serious mental illnesses [82-84]. The social drift theory on the other hand hypothesises that the symptoms and cognitive decline associated with these illnesses leads to difficulties in functioning and hence maintenance of living standards, thus leading to a drift into lower socioeconomic areas [81, 85]. Social drift can operate in the opposite direction too, with individuals without mental illness moving to affluent areas. Though the relationship is still debated, some consensus has been reached that social drift alone cannot explain the elevated rates of SMI in socioeconomically disadvantaged neighbourhoods. For example, a longitudinal multilevel study by Werner et al. (2007) demonstrated that individuals who develop schizophrenia in later stages of life were more likely to be born in deprived neighbourhoods [86] . Moreover, the evidence available on social drift process after illness onset is limited [87, 88]. In addition, a nationally representative longitudinal study

from South Africa demonstrated that both social causation and social drift act simultaneously reinforcing poverty-serious mental illness cycles [89] . Adding to the evidence for multi-causality, recent genetic based population studies report that genetic predisposition as well as interaction between individual and area level factors may also play a role in explaining the higher risk of SMI in deprived neighbourhoods [83, 90].

Neighbourhoods and Type 2 diabetes

A positive link has been established between cardiometabolic risk factors including diabetes and neighbourhoods [91-93]. A study by Cox et al. (2007) in Scotland, UK, reported that neighbourhood poverty is positively related to diabetes incidence [91]. Using data from the 'Moving to Opportunity study', Ludwig et al.(2011) identified a lower diabetes prevalence among lower income adults who moved from a high poverty neighbourhood to a lower poverty neighbourhood than those who were not offered the opportunity to move and remained in the high poverty neighbourhoods [94]. A cross sectional survey conducted among the 65651 patients of 61 general practitioners in Spain also reported a higher prevalence of type 2 diabetes and its chronic complications in patients of lower neighbourhood socioeconomic status (OR 2.17, 95 % CI 1.77 -2.28). This elevated risk in type 2 diabetes with rise in socioeconomic disadvantage was reported to be more marked in women compared to men in this study [95]. One Australian study investigated the association between area-level socioeconomic disadvantage and diabetes control in the Illawarra-Shoalhaven and found that the odds of poorer glycaemic control increased significantly with the increase in disadvantage (OR 1.62 , 95 % CI 1.52 – 1.73 for the most compared to the least disadvantaged neighbourhoods) [96].

Neighbourhood features have been extensively linked to the environmental risk factors for T2D such as physical inactivity, imprudent diet, stress and obesity [41, 97-102]. Studies from the Multiethnic Study of Atherosclerosis reported that living in a

neighbourhood with better physical activity and healthy food resources was associated with lower incidence of T2D [101, 103]. Sundquist et al. (2015) reported a negative association between neighbourhood-built environment such as walkability and T2D risk in a large sample of Swedish adults [104]. A study in Australia reported significantly lower incidence of type 2 diabetes in greener neighbourhoods after controlling for sociodemographic and cultural factors [105]. Neighbourhood social features such as safety and crime were also found to be associated with conditions related to diabetes such as obesity and lower physical activity [10, 106].

Neighbourhoods and Type 2 diabetes comorbidity in serious mental illness

Neighbourhood environments have been associated with both SMI and T2D as independent conditions [70, 72, 91, 96, 107]. However, research to date has not adequately investigated the association between neighbourhood features and SMI-T2D comorbidity. To the best of my knowledge, the only study prior to this thesis investigated major depression alone and reported a positive but non-significant association between neighbourhood level disadvantage and SMI-T2D comorbidity [108]. The aforementioned study nonetheless provided indicative evidence of higher attributable risk of T2D in disadvantaged neighbourhoods, opening the possibility of focusing on disadvantaged areas in order to reduce the risk of T2D in SMI.

People with SMI often experience low socioeconomic status [109] and consequently live in disadvantaged neighbourhoods, as these areas are more likely to offer affordable accommodation [8]. As posited by various theories incorporating the social determinants of health, neighbourhood level resources such as health care facilities, access to healthy foods and safe environments may be disproportionately less available in disadvantaged neighbourhoods [110]. This unequal distribution of opportunity structures is commonly referred to as ‘deprivation amplification’ [111] and may act as a risk for adverse health

behaviours such as sedentary life, unhealthy food choices and obesity which are implicated as the risk factors for T2D [8, 10, 101, 112]. It is also speculated that the economic instabilities associated with deprivation can induce chronic stress which can result in altered immune system response and activate the hypothalamic-pituitary-adrenal axis leading to diabetes [2, 113]. An association between neighbourhoods and comorbid diagnosis of SMI-T2D comorbidity is highly plausible, given what is known about the underlying mechanisms that drive these two disorders. Hence additional research on the association between neighbourhoods and SMI-T2D comorbidity is warranted, given the paucity of evidence available and the plausibility of an association.

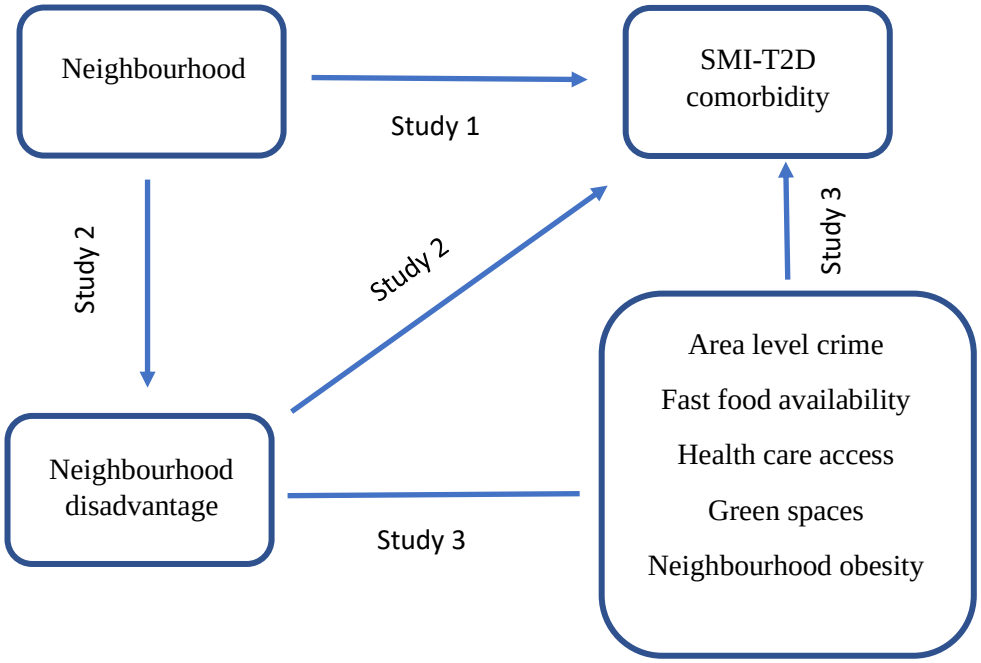
Aims and thesis outline

There is a lack of evidence regarding the association between neighbourhoods and SMI-T2D comorbidity. The primary objective of this study is to address this knowledge gap by investigating the associations neighbourhoods might have with SMI-T2D comorbidity. The specific aims of this research are to

1. Describe the geography of SMI-T2D comorbidity in the Illawarra-Shoalhaven region of NSW, Australia
2. Explore the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity
3. Evaluate the association between the neighbourhood contextual features of area level crime, access to health care services, availability of green spaces, neighbourhood level obesity, availability of fast-food outlets and SMI-T2D comorbidity

To address these aims, three empirical studies were undertaken using a combination of spatial and multilevel modelling methods, which are discussed further in Chapter 3. A conceptual framework describing the overall thesis is described in Figure 1.2

Figure 1. 1 : Diagrammatic representation of thesis



Study 1 addresses aim 1 of this thesis and describes the geographic variation in the distribution of SMI-T2D comorbidity in the Illawarra-Shoalhaven. Study 2 builds on the information gathered from study 1 to address aim 2 and examines the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity. Study 3 further extends the findings from study 2 by addressing aim 3 and investigates the association between specific features of disadvantaged neighbourhoods and SMI-T2D comorbidity. Neighbourhood features investigated in study 3 are neighbourhood level crime, accessibility to health care services, availability of green spaces, neighbourhood obesity, and fast food availability

Thesis Style and structure

This PhD study was funded by an Australian Government Research Training program and Illawarra-Shoalhaven Local Health District-University of Wollongong combined scholarship. This thesis has been prepared in journal article style format (Style 2) which fulfils the requirements of Doctor of Philosophy [114] and is presented as a series of manuscripts prepared for publication in peer reviewed journals.

This thesis is structured into 7 chapters including the current introduction chapter (Chapter 1). Chapter 2 details the systematic literature review undertaken as part of this research and chapter 3 describes the datasets and the key methodologies used. Chapter 4 presents the first study (Study 1) which describes the geography of SMI-T2D comorbidity in the Illawarra-Shoalhaven. Geographic convergence of SMI-T2D comorbidity with the single diagnosis of SMI and Diabetes is also examined in this chapter. Chapter 5 addresses the second aim of the research (Study 2) and explores the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity. Chapter 6 builds on study 2 and examines the association between neighbourhood contextual factors such as fast food availability, crime, access to health services, green spaces and neighbourhood obesity and comorbid diagnosis of SMI and T2D, accounting for neighbourhood level socioeconomic disadvantage (Study 3). Chapter 7 discusses major findings, implications and limitations from this body of work and is concluded with recommendations for future research and policy.

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CHAPTER 2

Literature review

The first part of this chapter is a systematic literature review, which was published in the *Journal of Primary care and Community Health,* titled as 'Serious mental illness, neighbourhood disadvantage and type 2 diabetes risk: a systematic review of the literature'. This review as it appears in print is available in the Appendix (Appendix A). The second part of this chapter reviewed and summarised the neighbourhood contextual factors that may be associated with SMI-T2D comorbidity.

Reference

Walsan, R., Bonney, A., Mayne, D. J., Pai, N., Feng, X., Toms, R., (2018). Serious mental illness, neighbourhood disadvantage and type 2 diabetes risk: a systematic review of the literature. *Journal of Primary Care & Community Health. 2018. Vol 9, doi: 10.1177/2150132718802025.*

Authorship details

Walsan (60%) – Conceptualisation, literature search, interpretation, drafting and reviewing final manuscript

Bonney (15%) – Supervision, interpretation and reviewing final manuscript

Mayne (10%) - Supervision, interpretation and reviewing final manuscript

Pai (5 %) - Supervision, interpretation and reviewing final manuscript

Feng (5 %) - Supervision, interpretation and reviewing final manuscript

Toms (5 %) – Literature search

Contribution to the thesis

This chapter systematically synthesised the body of literature examining the association between neighbourhoods and serious mental illness (SMI) – type 2 diabetes (T2D) comorbidity. The review was imperative to understand the evidence available on the association between neighbourhoods and SMI-T2D comorbidity and to further guide the research objectives of this thesis. The review identified a paucity of evidence in the research literature investigating the associations between neighbourhoods and SMI-T2D comorbidity, despite the plausibility of such an association and its implications for health. This review also provided a rationale for the selection and conceptualisation of a) serious mental illness, b) neighbourhood level variables and c) multilevel analysis used in the following chapters of this thesis

Serious mental illness, neighbourhood disadvantage and type 2 diabetes risk: a systematic review of the literature

Abstract

Aim: This review aims to systematically synthesise the body of literature examining the association between neighbourhood socioeconomic disadvantage and serious mental illness (SMI)–type 2 diabetes (T2D) co-occurrence.

Methods: We conducted an electronic search of four databases: PubMed; Scopus; Medline; and Web of Science. Studies were considered eligible if they were published in English, peer reviewed, quantitative and focussed on the association between neighbourhood disadvantage and SMI-T2D comorbidity. Study conduct and reporting complied with PRISMA guidelines, and the protocol is made available at PROSPERO (CRD42017083483).

Results: The one eligible study identified reported a higher burden of T2D in persons with SMI but provided only a tentative support for the association between neighbourhood disadvantage and SMI-T2D co-occurrence.

Conclusion: Research into neighbourhood effects on SMI-T2D comorbidity is still in its infancy and the available evidence inconclusive. This points to an urgent need for attention to the knowledge gap in this important area of public health. Further research is needed to understand the health resource implications of the association between neighbourhood deprivation and SMI-T2D comorbidity and the casual pathways linking them.

Introduction

Mental disorders that are severe in degree, persistent in duration and produce significant functional impairment are referred to as serious mental illness (SMI) [1]. Individuals with SMI have higher risk of premature mortality and a reduced life expectancy of approximately 10 to 30 years compared with the general population [2-4]. A large proportion of this excess mortality experienced by people with SMI is the consequence of cardiovascular diseases for which type 2 diabetes (T2D) is a major risk factor [4-6].

The prevalence of T2D in people with SMI is two to four times higher than the general population with a median estimate of 13 % [7-11]. The median prevalence rate of type 2 diabetes in general population is reported to be 6.4 % [12]. In those with SMI, a comorbid diabetes diagnosis not only confers a higher cardiovascular risk and increased mortality but is also associated with increased hospitalisations, greater number of emergency department visits, non-adherence to treatments, higher healthcare utilisation costs, and decreased quality of life [7, 9, 10, 13-15]. Studies have reported that people with both schizophrenia and type 2 diabetes have worse cognitive deficit than schizophrenia without diabetes or diabetes alone, which can significantly impede their social rehabilitation and lead to poor clinical and functional outcomes [16, 17].

Numerous studies have established that people who live in disadvantaged environments have worse mental and physical health outcomes than people living in advantaged areas [18-24]. This phenomenon is commonly referred to as the social gradient of health [25] and is expected to be heightened for people with SMI due to their complex needs [26]. People with mental illness often live in disadvantaged neighbourhoods [27]. Lack of adequate health care facilities, decreased access to healthy foods and an unsafe environment in these neighbourhoods are often associated with adverse health outcomes

such as sedentary life, unhealthy food choices and obesity [28-31] which are the major risk factors for T2D [32, 33]. It is also proposed that the economic uncertainties associated with deprivation can induce chronic stress which can result in altered immune system response and activate the hypothalamic pituitary adrenal axis leading to diabetes [10, 34]. An association between neighbourhoods and comorbid diagnosis of SMI and T2D is highly plausible, given what is known about the underlying complex mechanisms that drive these two disorders.

Neighbourhood disadvantage has been associated with SMI and T2D [22-24, 35-37]. However, only a few studies have examined the associations between neighbourhood disadvantage and chronic disease comorbidities [38, 39]. There is increasing interest in recent years to address diseases that occur concurrently rather than as separate conditions; that is, are comorbid. Moreover, 'Syndemics', which is gaining broad recognition in public health literature, also calls for a holistic approach that considers the biological and social interactions of two or more synergistic diseases rather than treating them as separate entities independent of the social context in which they are found [40].

Given the importance and the degree of public health burden imposed by SMI-T2D comorbidity and the plausibility of an association with neighbourhood deprivation, it is imperative to understand the evidence available on the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity. Understanding these relationships would be useful in developing evidence based holistic interventions, health care policies and would even help us in designing healthier life spaces. Accordingly, this review aims to synthesise the body of literature examining the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity

Methods

Design

This systematic review followed the Preferred Reporting Items for Systematic review and meta-analysis (PRISMA) format. Research question, inclusion and exclusion criteria and search strategy were developed before the review process based on the PICO (Population, Indicator, Comparison and Outcome) approach. The protocol for this systematic review was registered on PROSPERO (CRD42017083483) and can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=83483.

Search strategy

Relevant literature was identified through a systematic search of four databases: PubMed; Scopus; Medline; and Web of Science. These databases were selected due to their relative strengths and coverage in medical and social sciences. An initial text search was carried out on PubMed to identify all the possible synonyms of the main concepts and keywords included in the study.

The search strategy consisted of three themes: neighbourhoods (neighborhoods, neighbourhoods, residence characteristics, community, small area, context or geography); type 2 diabetes (type 2 diabetes, type 2 diabetes mellitus, non-insulin dependent diabetes mellitus); and serious mental illness (serious mental illness, psychosis, schizophrenia, bipolar disorder, major depression, affective disorders, psychotic disorders) (see Table 2.1). The population included in the literature search, i.e. individuals diagnosed with a serious mental illness, corresponded to the International Classification of Diseases (ICD)10 codes F20 – F39 [1]. The reference lists of retrieved articles were hand searched to identify relevant articles that may have been missed in the electronic search. No geographic, date or study- design restrictions were imposed.

Table 2. 1 : Search terms and subject headings in PubMed format (modified in other search engines)

Search	Query
#1	neighborhood [Title/Abstract] OR neighbourhood [Title/Abstract] OR "residence characteristics" [Title/Abstract] OR community [Title/Abstract] OR "small area" [Title/Abstract] OR context [Title/Abstract] OR geography [Title/Abstract]
#2	"serious mental illness" [Title/Abstract] OR psychosis [Title/Abstract] OR schizophrenia [Title/Abstract] OR "bipolar disorder " [Title/Abstract] OR "major depression" [Title/Abstract] OR "affective disorders" [Title/Abstract] OR "manic depression" [Title/Abstract]
#3	"type 2 diabetes" [Title/Abstract] OR "type 2 diabetes mellitus" [Title/Abstract] OR "non-insulin dependent diabetes mellitus" [Title/Abstract]
# Final Search	# 1 AND #2 AND #3

Study selection

Journal articles that met the following criteria were included in the study: published in English; peer reviewed; quantitative; and focussing on the neighbourhood disadvantage and SMI-T2D comorbidity. Various aspects of neighbourhood socioeconomic disadvantage that were commonly included in research literature [41, 42] and were empirically associated with type 2 diabetes [43] were considered in this review. This included composite measures of disadvantage as well as its predictors such as poverty, racial segregation, unemployment, education, housing, crime, and social disorder. Studies

were checked inductively for neighbourhood socioeconomic constructs, whether the article authors acknowledging it as a measure of disadvantage or not. Studies reporting SMI and T2D independently and not as comorbid conditions were excluded from the review. Similarly, studies pertaining to neighbourhood features other than disadvantage were also not included.

A three-step study selection process was employed. In the first step, articles were screened, and duplicates were removed. In the second step, the titles and abstracts of remaining articles were reviewed for their eligibility for inclusion. In the third step, eligible articles identified were examined in full for their inclusion in the review. Two reviewers (RW and RMBST) independently performed all three stages. The studies were excluded for the following reasons: did not examine neighbourhood socioeconomic disadvantage (42), not a quantitative study (1), did not involve comorbidity (16). Study selection procedures are summarized in Figure 2.1.

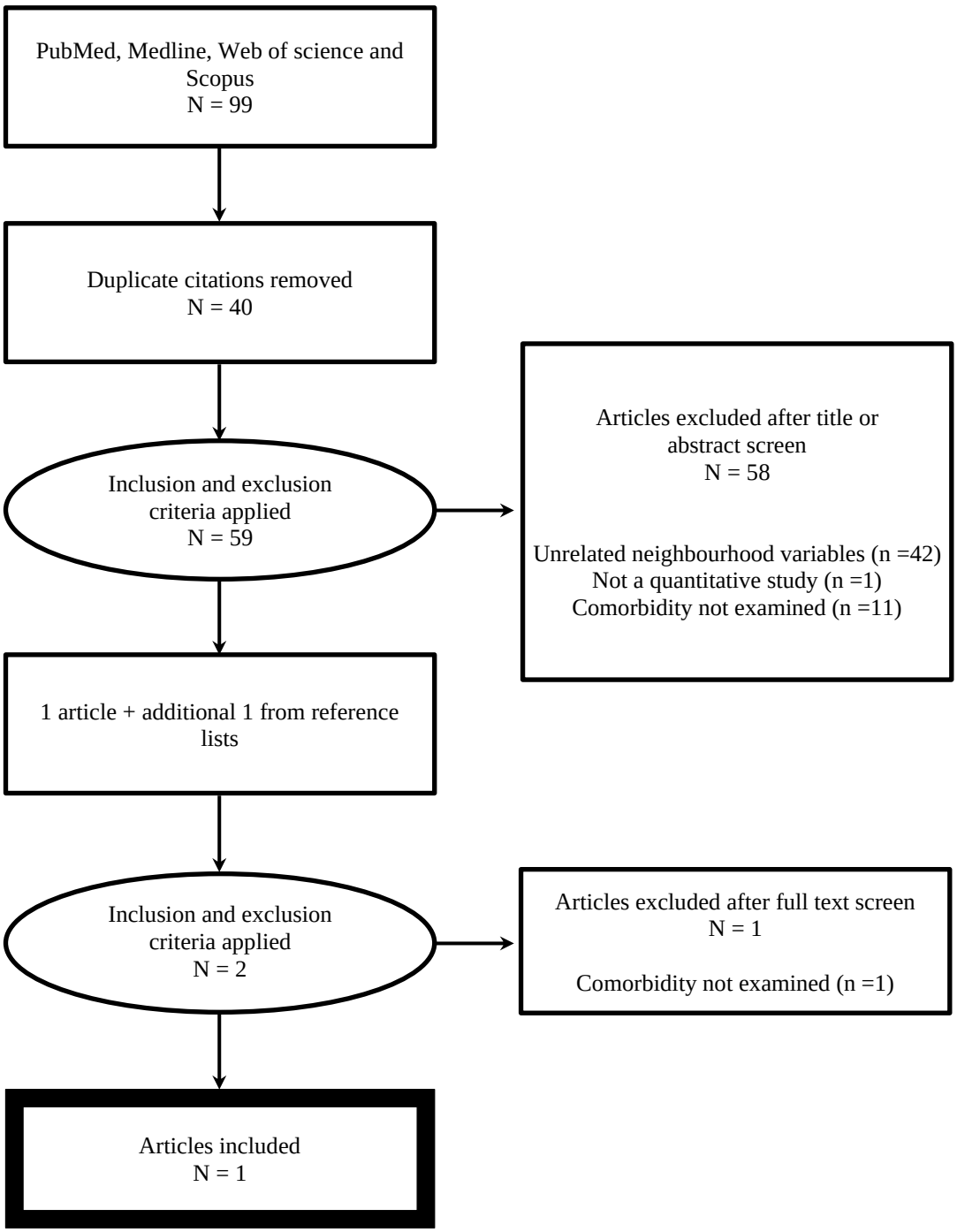
Data extraction

Information extracted from the eligible studies included the following: author; publication date; country of data origin; study population; study design; measures of neighbourhood disadvantage; measures of type 2 diabetes; method of analysis; and major findings.

Data analysis

As the focus of this review was to describe the association between neighbourhood disadvantage and SMI-T2D comorbidity, the data analysis concentrated on this association. Meta-analysis was thought to be inappropriate due to the heterogeneity expected between the study populations, design and neighbourhood measures. Hence a descriptive review was conducted.

Figure 2. 1: Flowchart of literature search process and the results



Results

The literature search retrieved a total of 99 potentially relevant records. After excluding 40 duplicates, the remaining 59 articles were screened for their broad eligibility, and a further 58 ineligible articles were excluded. The one remaining article and the additional

one retrieved from reference list were reviewed in full. One article was excluded after full text review leaving one eligible study for inclusion in the review. Study selection outcomes at each stage of the review are summarised in Figure 2.1.

The one study meeting the selection criteria examined the association between neighbourhood disadvantage, major depression and type 2 diabetes risk among 336,340 adults from Sweden (Table 2.2). The study relied on identified incident diabetes in those individuals with clinically diagnosed major depression and had a follow up period of seven years. The measure of neighbourhood disadvantage used in the study was a computed index based on four variables: income; education; unemployment; and social service assistance. Multilevel logistic regression models were used to assess the relationship between disadvantage and comorbidity.

Table 2. 2 : Summary of studies on neighbourhood disadvantage and SMI-T2D comorbidity

Number	1
Study	Mezuk et al., 2013 [44]
Country	Sweden
Sample	336,340 adults
Study design	Longitudinal
SMI measure	Clinically diagnosed major depression from primary care, inpatient or outpatient registries from January 2001 to December 2007

Neighbourhood disadvantage measure	Computed composite index based on education status, income, unemployment and social welfare assistance.
Type 2 diabetes measure	Clinically diagnosed type 2 diabetes from primary care, inpatient or outpatient registries, or the use of antidiabetic medications as recorded in primary care/national prescription registries.
Method of analysis	Multilevel analysis
Findings	Depression was significantly associated with T2D risk (OR 1.10, 95% CI 1.06 -1.14). Similar relationship was observed for neighbourhood disadvantage (OR high vs low 1.67, 95 % CI 1.57 -1.77). However, the interaction term between depression and disadvantage was found to be non-significant (Intra class correlation 0.013).

After accounting for demographic and individual characteristics, such as age, gender, family income, educational attainment and immigration status, the interaction between neighbourhood disadvantage and comorbidity risk was found to be non-significant (β 0.01, 95% CI -0.06 - 0.06, p = 0.573) indicating that association between major depression and T2D is similar across different levels of neighbourhood disadvantage. Although there was no evidence of synergistic interaction, the attributable risk of type 2 diabetes due to depression (Diabetes incidence $_{\text{depression}}$ − Diabetes incidence $_{\text{without depression}}$) was increased in high deprivation areas (16.4) compared to lower deprivation areas (8.2). The study also

highlighted that the individual socioeconomic indicators were not strongly related to T2D risk after controlling for neighbourhood factors, indicating the role that contextual factors may play in the development of comorbid association.

Discussion

Our review indicates a paucity of evidence in the research literature investigating the associations between socioeconomic disadvantage and comorbidity of SMI and T2D despite the plausibility of such an association and its implications for health. The only research available reports a non-significant association between socioeconomic disadvantage and SMI-T2D co-occurrence [44]. However, the above study focussed entirely on major depression which is often claimed to be under detected especially in the primary care settings [45] and did not consider other forms of SMI such as schizophrenia or bipolar disorder. The study however provides indicative evidence of higher attributable risk of T2D in disadvantaged neighbourhoods, signalling the focus needed on high deprivation areas in order to reduce the risk of T2D in SMI patients. Further, the study provides an impetus to explore potential neighbourhood contextual pathways linking neighbourhood deprivation with SMI-T2D comorbidity.

Previous research examining the association between neighbourhood disadvantage and T2D risk as an independent condition has established a consistent positive association, whereby increased neighbourhood deprivation is associated with increased T2D risk [46-48]. Research has also shown that multimorbidity is common among populations living in deprived neighbourhoods [38]. Although this large cohort study provides only a tentative support for the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity, it is consistent with observations showing a high burden of

T2D in persons with SMI. More research is needed under different settings and including different forms of SMI to confirm the above results.

Another limitation in the evidence base is that the available study focussed mainly on the social aspect of neighbourhood disadvantage and used a computed index of disadvantage based on income, education, unemployment and social service assistance and did not focus on the contextual factors of the neighbourhoods which might play a significant role. For example, deprived neighbourhoods often lack access to fresh produce, and may be dominated by fast food and convenience stores, making the latter the easily available food option [18]. Similarly, deprived neighbourhoods might lack an environment conducive to physical activity [14]. The presence of such unobserved moderating or mediating factors might have also contributed to the non-significant association between the two in the above study.

The lack of a conclusive evidence base makes it difficult to make firm policy recommendations based on our review. Further research is needed to capture the completeness of association between neighbourhood deprivation and SMI-T2D comorbidity, and the causal pathways linking them. Future research should also focus more on the modifiable contextual or physical aspects of the area that could potentially mediate or moderate the association between deprivation and SMI-T2D comorbidity. Sound knowledge of the factors that are modifiable by interventions will turn out to be more useful and informative for developing policy solutions and interventions.

Conclusions

Research into neighbourhood effects on SMI-T2D comorbidity is still in its infancy, and the available evidence inconclusive. This points to an urgent need for attention to the knowledge gap in this important area of population health. Further research is needed to

understand the health resource implications of the association between neighbourhood deprivation and SMI-T2D comorbidity and the casual pathways linking them. Multilevel study designs can generate more evidence in this direction as it can be useful in analysing the moderating and mediating processes between neighbourhood and individual level variables. Identifying the relationship and connecting processes will help policy makers to develop efficient intervention strategies to curb the Syndemics of SMI and T2D.

Neighbourhood contextual factors and T2D comorbidity in SMI

Contextual variables are defined in this thesis as the broader social and physical opportunities of the neighbourhoods over and above the characteristics of its individual residents [49]. A preliminary literature review was carried out to identify the relevant neighbourhood contextual indicators of T2D risk in SMI. There were few studies looking at the association between neighbourhood features and T2D in the context of SMI, hence the review was mainly focussed on studies with T2D as a single condition. The only study available in this direction, explored the associations of psychosocial and socioeconomic adversity on SMI-depression comorbidity in Latinos and reported a significant positive association between neighbourhood crime and comorbidity [50]. The above study reported a 53% increase in odds for having diabetes and high-level depressive symptoms with one standard deviation increase in neighbourhood level crime and violence. The neighbourhood problems examined in this study were however self-reported and may have been influenced by the negative cognitive-emotional biases associated with depression. Moreover, the aforementioned study examined only Latino population and was focussed only on depression-T2D comorbidity.

Neighbourhood characteristics have been extensively linked to traditional risk factors of T2D (as a single condition) such as physical inactivity, poor-quality diet, stress, and obesity [32, 51-53]. Some studies have investigated more specific features of neighbourhood environments in relation to T2D risk. For example, reports from the Multiethnic Study of Atherosclerosis indicated that living in a neighbourhood with better resources for physical activity and healthy food was associated with lower incidence of T2D during 5 years of follow-up [32]. This association was reported to persist even after controlling for individual level variables such as age, sex, family history, socioeconomic status etc and slightly reduced after additional adjustment for baseline body mass index

(BMI). Another longitudinal study examining the same cohort, also reported a lower risk of developing T2D with greater exposure to neighbourhood healthy food (HR 0.88, 95 % CI 0.79 – 0.98) and physical activity resources (HR 0.79, 95 % CI 0.71 – 0.98) [54]. Sundquist et al (2014) reported negative associations between neighbourhood walkability and T2D risk in a large sample of Swedish adults (OR 1.33, 95 % CI 1.13 – 1.55 in the lowest walkable decile versus highest) [55]. However, this association no longer remained statistically significant after adjustment for individual socio-demographic variables.

Neighbourhood crime is reported as an important contributor to disparities in cardiovascular outcomes, including diabetes [56, 57]. A longitudinal study from Australia reported a positive association between perceived neighbourhood level violent crime and diabetes (OR=1.44, 95 % CI 1.12 – 1.87) [58]. Another cohort study also reported similar association between perceived area level crime and metabolic syndrome, which was found to be mediated by physical activity (OR 1.15, 95 % CI 1.01 – 1.31) [58]. Previous research has also shown that the residents of neighbourhoods with high crime rates are less likely to be physically active [30]. Physical inactivity may contribute to greater T2D risk in individuals with SMI [7]. Crime is also reported to increase stress and influence psychosocial outcomes [59, 60]. It is proposed that chronic stress can lead to altered immune system response and activate the hypothalamic pituitary adrenal axis leading to T2D [10, 34]. Area level crime may hence compound the experiences of psychosocial stress experienced by individuals with SMI [61]. Residents' beliefs, or perceptions, about the safety of their neighbourhood were also shown to influence their behaviour thus influencing T2D risk [58, 62].

Proximity to greenspace has been previously linked to increased physical activity and lower risk of obesity and T2D [63-65]. A longitudinal study showed that longer exposure

to green space is associated with reduced risk of diabetes, mainly through its effect on physical activity (HR 0.87, 95 % CI 0.78 – 0.98) [66]. A recent systematic review also identified a negative association between increased green space exposure and type 2 diabetes using a meta-analysis of six longitudinal studies (OR 0.72, 95 % CI 0.61 – 0.85) [67]. Research has also shown that green spaces can provide stress relief and provide an opportunity for social mixing which can be beneficial for people with SMI [68]. Less green space in people's neighbourhood was found to coincide with feelings of loneliness and perceived shortage of social support, which in turn was found to mediate the relationship between green space and health [69].

A growing number of studies have consistently found that health care access is strongly tied to positive physical and mental health outcomes [70-72]. Greater access to primary care was shown to reduce the association of income inequality and health especially in areas with greater disadvantage [73]. A narrative review by Moore et al reported inequitable access in physical health care for people with schizophrenia [74]. For people with SMI, regular interactions with health service providers are required for disease management as well as for earlier detection and prevention of T2D [75, 76].

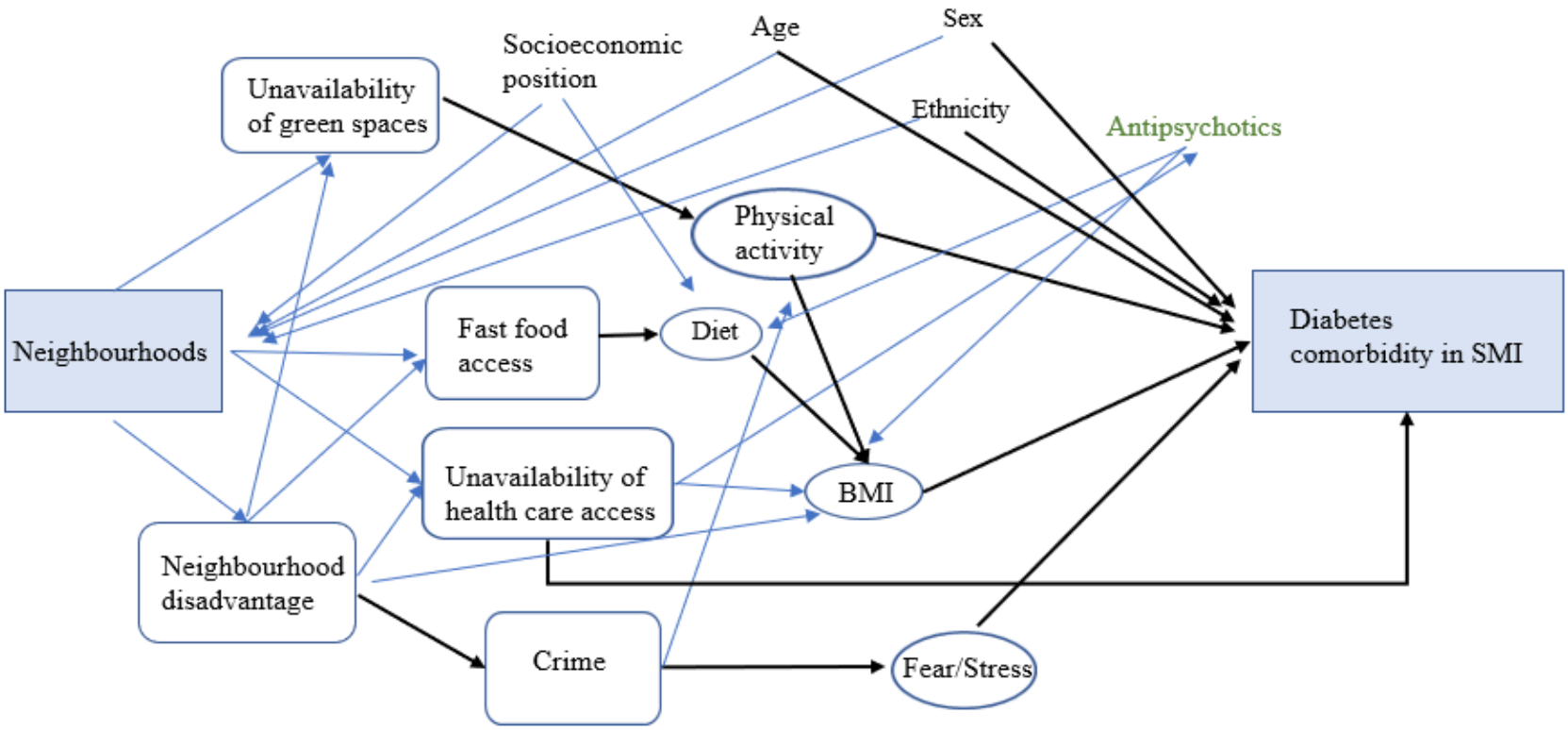
Access to high-density fast-food outlets is positively associated with unhealthy food behaviours that can have detrimental effects on BMI and T2D risk [77-79]. A population-based cohort study from Canada showed a greater risk of incident diabetes associated with greater proportion of fast-food outlets relative to all restaurants in a five year follow up (HR 1.79, 95 % CI 1.03 – 3.12) [80]. A study from UK also reported significantly increased odds for diabetes associated with more fast-food outlets even after adjustment for individual level variables (OR 1.02, 95 % CI 1.00 – 1.04) [81]. Differential availability of local area fast food stores by neighbourhood characteristics such as disadvantage may contribute to the differential prevalence of obesity, and subsequent T2D in people with

SMI. Individuals with SMI may be more vulnerable to differential access to healthy food due to their lower income, inability to travel and physical and psychological limitations for food shopping [26].

Individuals with SMI are more likely to live in and be exposed to neighbourhood environments that exacerbate T2D risk such as higher concentration of fast food outlets, lack of health care resources, and unsafe environments due to their lower socioeconomic status [22, 27]. These contextual features may compound the experiences of psychosocial stress and encourage participation in adverse health behaviours such as unhealthy eating, physical inactivity, and excess weight gain, all of which can contribute to T2D risk.

A directed acyclic graph (DAG) was developed based on the literature review above to identify the observed relationships between neighbourhoods and SMI-T2D comorbidity and the potential confounding variables for statistical adjustment, as shown in Figure 2.1 [82]. An arrow from one factor to another depicts an association, while a bold arrow indicates a plausible causal relationship [83]. Neighbourhood exposures are depicted in rounded rectangles and associated behaviours are depicted in the circular nodes. Unboxed variables are the confounders identified requiring adjustment. Variables that are beyond the scope of the study such as antipsychotic medications are also included in this graph due to their known influence on the outcome (shown using different coloured font). Casual inference was beyond the scope of this research due to its cross-sectional study design.

Figure 2. 2: DAG specifying the impact of neighbourhoods on SMI-T2D comorbidity



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CHAPTER 3

Data and methodology

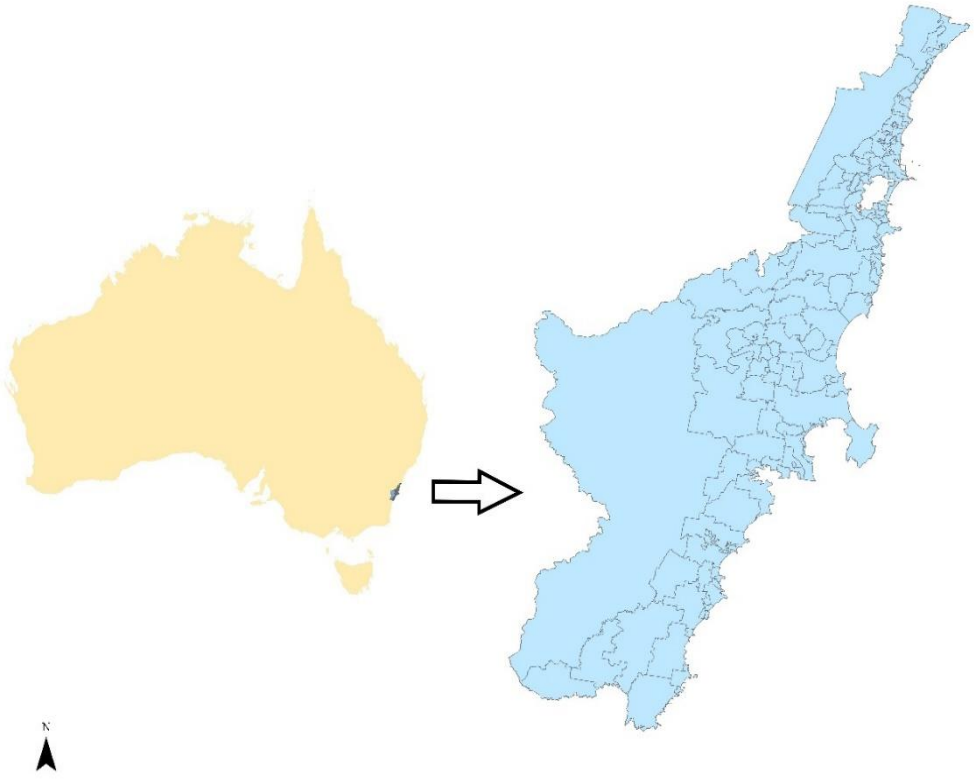
This thesis aimed to explore the association between neighbourhood characteristics and T2D comorbidity in SMI over and above individual level risk factors. A combination of spatial and multilevel modelling methods were adopted to achieve Aims 1 - 3. The chapters 4, 5 and 6 of this thesis, which are presented in article format, each contain a methodology section. The level of methodological details provided in those papers are necessarily limited due to journal word count restrictions. This chapter provides a more detailed description of the research methods used in this thesis.

Research design and setting

This cross-sectional study was carried out in the Illawarra-Shoalhaven regions of New South Wales (NSW), Australia, which had an estimated resident population of 368,604 people at the time of the 2011 Australian Census [1]. ta from the southern outskirts of Sydney (Wollondilly and Sutherland shires) to the south coast of NSW (North Durras), and is bounded by the Tasman sea on the east and mountainous Illawarra escarpment on the west (Figure 3.1). The grey lines in the map depicts the state suburb boundaries used in this study. The region is the third largest regional economy in NSW [2] and encompasses the four local government areas of Kiama, Shellharbour, Shoalhaven and Wollongong [3]. The area has a mix of rural and urban characteristics and the population distribution also varies considerably between the areas. The densely populated areas are mainly found along the eastern coastal line. Wollongong, the main metropolitan city centre in the study area is geographically located towards the north eastern part of the study area. The socioeconomic profile of the study area is comparable to that of NSW and Australian averages [4, 5].

As this was one of the first studies to investigate the association between neighbourhoods and SMI-T2D comorbidity, the hypotheses were more exploratory in nature and aimed to identify and establish links between neighbourhoods and SMI-T2D comorbidity. Power calculations for the hypothesis was not set up prior to analysis but was observed post hoc based on the significant results (observed power) and the study size reflects the available study population during the study period of interest.

Figure 3. 1: Map of Australia showing the study area



Neighbourhood unit

State suburbs (SSC) were used as the neighbourhood proxy in this study as it was the smallest unit at which health service data were available. The boundaries used were the

2011 Australian Statistical Geography Standard (ASGS) [6]. State suburbs are the Australian Bureau of Statistics (ABS) approximation of suburbs gazetted by the office of Geographic Names Board [6]. The study region comprised of 167 suburbs with an average land area of 36.56 km^2 and 2207 residents each [1].

Data

Individual level data and the outcome variable

Serious mental illness (SMI) and SMI-T2D comorbidity data utilised in this study came from the electronic health records of Illawarra Shoalhaven Local Health District (ISLHD). The data were extracted from the Illawarra Health Information platform (IHIP) which is a research partnership instituted between ISLHD and the University of Wollongong for providing ISLHD data to researchers. Serious mental illness in this study was defined as any primary or secondary diagnosis of SMI in the Admitted Patient Data Collection (APDC) records, which records the inpatient activities. Data extraction was based on the 10^{th} version of the International Classification of Diseases Australian Modification (ICD10 AM) and covered the period 2010 to 2017 [7]. Eligible diagnostic groups included, and their respective ICD10 AM codes, are presented in Table 3.1. Extraction was restricted to SMI individuals who were 18 years and over.

Data on SMI were initially retrieved from both inpatient and community mental health services. Community service data were not included in the study analysis as there were concerns regarding the extent of coding adopted in community services to document T2D comorbidity information. Inpatient stays record included all the diagnostic ICD-10-AM codes to capture SMI and has been previously reported to be accurate with regard to T2D comorbidity documentation, with an accuracy of 87 % [8, 9]. Data from private mental health services were also not available for this study. It is a potential limitation of this

thesis that data sourced only from inpatient mental health records were used. Even though this is supported by the data from the Australian National Surveys of Psychosis (indicating that 45.6 -62.9% of people with SMI reported ≥1 hospital admission for any reason in the previous 12 months) [10], the results from this study may not be generalisable as it was based on a specific cohort of patients from public hospital facilities.

Table 3. 1 : SMI diagnosis and ICD 10 codes included in the study

Diagnosis	**ICD10 AM codes**
Schizophrenia	F20
Other non-affective psychosis	F22 – F29
Bipolar disorder	F30, F31
Major depression	F32, F33
Other affective disorders	F34, F39

The primary outcome of interest in this thesis was SMI-T2D comorbidity. It was defined as having a recorded T2D diagnosis (E11) in individuals with SMI and was extracted as either present or absent along with each of the SMI records.

Community derived diabetes data (Gen DM) used in chapter 4 for comparing the geographic convergence were accessed from the Southern IML Research (SIMLR) Study database for the period of 2010 to 2014. The SIMLR Study is a longitudinal, community-derived and geographically referenced database comprising of a near-census routinely collected pathology results by the largest pathology service provider covering the

Illawarra-Shoalhaven and includes residents 18 years and over [11]. The community-derived diabetes sample used in this study consisted of individuals with at least one haemoglobin A1c (HbA1c) test between 2010 and 2014 and an HbA1c result ≥ 6.5 % or plasma glucose levels ≥7.0mmol/L within 12 months of an HbA1c test. This was consistent with thresholds for diabetes diagnosis used in the Australian National Health Measures Survey [12].

All the data extracted in this study were deidentified, conforming with the requirements of the Privacy Act 1988 (Cth) and Health Records and Information Privacy Act 2002 (NSW). Data linkage was not an option as datasets were completely deidentified. Information on the population of the region was obtained from the 2011 Australian Census of Population and Housing [1]

Individual sociodemographic characteristics extracted were continuously measured age, gender and country of birth information. Age was categorized into three groups: young adults between 18 - 44 years; middle-aged between 45 - 65 years; and older adults above 65 years. This categorisation was in accordance with sociological and epidemiological life course framework of different stages of life [13]. However, in chapter 4 of this thesis, age was categorised into four groups: 18 - 34; 35 - 49; 50 - 64; and 65+ years. Gender was categorised as male or female. Country of birth details were grouped, based on the Standard Australian Classification of Countries produced by the Australian Bureau of Statistics [14]. The categories for country of birth were Australia; Oceania excluding Australia; United-Kingdom and Ireland; Western Europe; Eastern and Central Europe; South East Asia; Central and South Asia; Middle East and North Africa and Americas. Other variables which may have been relevant, such as individual socioeconomic status, ethnicity, age at diagnosis, number of hospital admissions and antipsychotic medication use, were unfortunately not available for this research.

Neighbourhood level data

Area level data used in this study were neighbourhood level socioeconomic disadvantage and five other contextual variables: (i) neighbourhood level crime; (ii) accessibility of health care services; (iii) neighbourhood green space; (iv) neighbourhood level obesity; and (v) availability of fast food outlets. The selection of explanatory variables included in this thesis was guided by the literature review in chapter 2. A directed acyclic graph described in chapter 2 further illustrated the potential relationships between the explanatory variables and SMI-T2D comorbidity and helped to identify sources of confounding requiring adjustment in statistical analysis.

Neighbourhood socio economic disadvantage

Chapter 5 of this thesis examines the association of neighbourhood socioeconomic disadvantage on SMI-T2D comorbidity. Neighbourhood socioeconomic disadvantage was operationalised using the Index of Relative Socioeconomic Disadvantage (IRSD) from the 2011 Socioeconomic Indexes for Area (SEIFA) by the Australian Bureau of Statistics (ABS) [5]. A regions IRSD score reflects its area-level socioeconomic disadvantage measured on the basis of 17 variables including education, income, occupation, unemployment, housing type, overcrowding and English proficiency [5]. For this study, IRSD scores for the Illawarra-Shoalhaven neighbourhoods were divided into quintiles of neighbourhood disadvantage with Quintile one (Q1) representing the 20% most disadvantaged suburbs in the Illawarra-Shoalhaven and Quintile five (Q5), the least disadvantaged 20%. While it is a potential limitation that the index scores from 2011 were used to cover the entire study period, an examination of the strength of agreement between 2011 and 2016 neighbourhood disadvantage quintiles using weighted kappa analysis

revealed a good agreement between the two (k = 0.80), indicating that the deprivation scores have stayed relatively similar during these periods [15].

Neighbourhood level crime

Annual area level police recorded crime counts were obtained from the NSW Bureau of Crime Statistics and Research (BOSCAR) for 2010 to 2017. Crime types considered were non-domestic violent assaults; homicides; malicious damage to properties; abduction and kidnapping; robbery and theft. These crime types have been associated previously with physical inactivity [16]. Average crime counts per neighbourhood were standardized to counts per 1000 people using the population data from the 2011 Australian Census of Population and Housing [1].

Accessibility to health care services

Health care access is influenced by several factors, but the two factors that are considered critical are the availability of health care services (supply) and the population (demand) [17]. Both these factors are considered to be spatially distributed [18]. Due to this, I focused on the spatial accessibility of health care resources in this thesis. Health care services data were extracted from the National Health Service Directory (NHSD) available from the Australian Urban Research Infrastructure Network (AURIN) database for the year 2016 [19]. Historical data on health care services for the study period were unavailable.

Accessibility was computed for primary care services, hospital services and mental health services in the Illawarra-Shoalhaven. A geographic information system (GIS) [20] based, two-step floating catchment area method (2SFCA), that explicitly considers health care service supply and population demands and their interactions within a catchment was adopted to calculate their accessibility [17]. In the first step, a 15 km distance catchment,

corresponding to 30 minutes travel time [21, 22] was placed around each health care service provider, and a provider to population ratio was computed and assigned to these health care facilities. The population of the entire suburb is included in these calculations if its centroid falls within a health service catchment. In the second step, a similar floating catchment was placed over the suburb centroid and all health care services falling in the area were identified. Accessibility was computed by summing all provider to population ratios contained within the catchment. Higher scores reflected improved accessibility. A sensitivity analysis with 10 km catchment window did not change results significantly. This method has been widely applied in health care access research around the world [21, 23, 24]. However, a major drawback with this approach is the assumption of constant access for all the population locations within the catchment and no access for populations outside the catchment [17, 25]. Several enhancements have been proposed to 2SFCA such as applying multiple travel time zones [24] and weighting by a decay function within each catchment [26, 27]. However, these could not be incorporated into this research due to the lack of availability of road network data. Computed spatial accessibility scores were classified into quintiles prior to analysis, with higher quintiles representing improved access.

Neighbourhood green space

Green space is included as a neighbourhood variable in chapter 6 and the data were obtained from AURIN database for the period of 2016 [19] and included green areas such as parks, reserves, national parks, conservation areas, forest reserves, recreational areas and other open spaces. The proportion of green space per neighbourhood unit was calculated using the spatial join tool of ArcGIS. Green space availability was classified as quintiles for further analysis and assigned to each record based on the patient's neighbourhood of residence. It is possible that green space data used in this study excludes

some smaller or informal green areas. However, smaller green areas are not considered a significant contributor to health and obesity outcomes compared to larger green spaces [28]. The potential for temporal misalignment is also acknowledged for this neighbourhood variable as 2016 data were used.

Neighbourhood Obesity

Obesity is a prevalent observation in people with SMI and is a major risk factor for T2D [29, 30]. Obesity was used as a contextual variable in this thesis as the information on individual-level obesity was not available for the study sample. Moreover, neighbourhood environments are reported to provide cues that support social norms defining individuals' behaviours, which can be compromised in higher obese neighbourhoods [31]. Hence the contextual effect of neighbourhood level obesity was considered as an independent variable in chapter 6. Neighbourhood level obesity was operationalised in this thesis as the percentage of population obese in each neighbourhood. Body mass index (BMI) cut off for obesity used was the World Health Organisation (WHO) threshold of BMI $\geq$30 kgm^{-2} [32]. BMI data were extracted from the SIMLR study database for the period of 2010 to 2014. Obesity percentage calculated was also classified into quintiles similar to other neighbourhood variables.

Availability of fast food outlets

In this thesis, fast food outlets were defined as service establishments that sell quickly prepared food with payment made prior to receiving food and with little table service [33]. Fast food data were sourced initially from Open Street Map (OSM) [34]. However, several discrepancies were observed between the data and the known availability of fast food outlets in the Illawarra-Shoalhaven. Hence fast food outlet information was confirmed using company websites and yellow pages and was extensively cross-checked

and verified [35]. Missing outlets were geocoded and added to the downloaded dataset. A population scaled measure of fast food density (number of fast food outlets per 10,000 people) was computed based on the population counts from 2011 Australian Census of population and housing [1]. Fast food density variables computed for suburbs were further collapsed into binary units (Not available, and available) as there were many suburbs with zero outlets.

Statistical overview

Preliminary analysis

Preliminary analysis was carried out to identify the characteristics of the sample and the key variables. A total of 4180 unique records were extracted with an SMI diagnosis between 1 January 2010 and 31 December 2017 based on the eligibility criteria. Individuals residing outside the study area (n = 50) and records with no suburb information (n = 283) or country of birth information (n = 8) were excluded from the analysis resulting in a final SMI sample of 3816 individuals. Of these, 463 (12.09%) had a T2D comorbidity. The community-derived diabetes sample for the Illawarra-Shoalhaven consisted of 13142 unique individuals. Data for the entire study period (2010 - 2017) was pooled to ensure sufficient counts. All the descriptive statistics were completed using R version 3.5 [36].

Description of the study sample

The overall description of the SMI and SMI-T2D comorbidity samples is given in Table 3.2. The purpose of this table was to describe the comorbidity sample as they relate to the key variables of this thesis.

Table 3. 2 : Descriptive characteristics of the study population

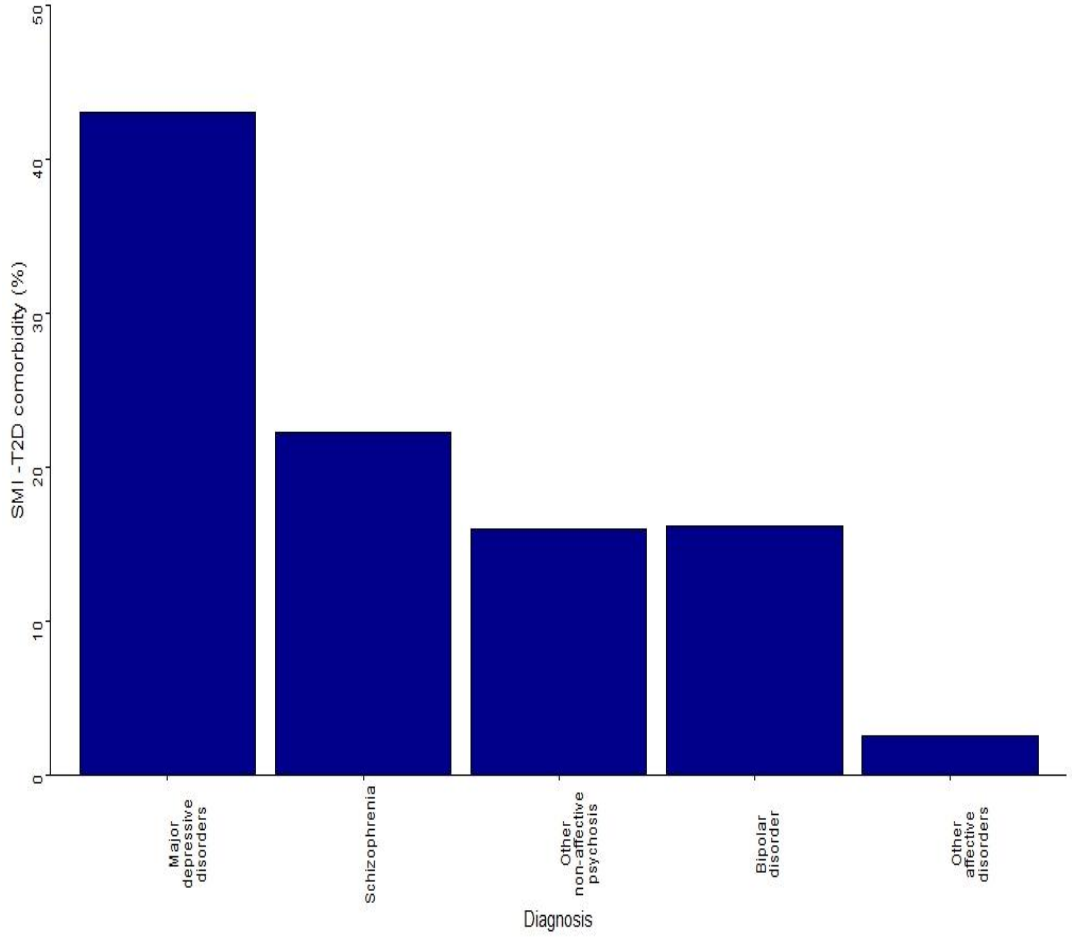
Variables	Individuals with SMI n = 3816	Individuals with SMI-T2D comorbidity n = 463	% comorbidity
Individual variables			
Gender			
Female	1848 (48.4 %)	245 (52.9 %)	13.3 (12.2 - 14.4)
Male	1968 (51.6 %)	218 (47.1 %)	11.1 (10.1 - 12.1)
Age, years (Mean (SD))	43.6 (18.5 %)	58.8 (15.7 %)	
Age, years			
18 – 44	1961 (51.4 %)	92 (19.9 %)	4.7 (4.0 - 5.4)
45 – 65	1213 (31.8 %)	193 (41.7 %)	15.9 (14.7 - 17.1)
65+	642 (16.8 %)	178 (38.4 %)	27.7 (26.3 - 29.1)
Country of birth			
Australia	3104 (81.3 %)	339 (73.2 %)	10.9 (9.9 - 11.9)
Oceania excluding Australia	74 (1.9 %)	12 (27.9 %)	16.2 (15.0 - 17.4)
UK & Ireland	212 (5.6 %)	35 (7.6 %)	16.5 (15.3 - 17.7)
Western Europe	137 (3.6 %)	29 (6.3 %)	21.2 (19.9 - 22.5)
Eastern and central Europe	125 (3.3 %)	29 (6.3 %)	23.2 (21.9 - 24.5)
North East Asia	17 (0.45 %)	0 (0.0 %)	0.0 (0.0 - 18.4)
South East Asia	51 (1.3 %)	6 (1.3 %)	11.8 (10.8 - 12.8)
Central and South Asia	16 (0.4 %)	3 (0.6 %)	18.8 (17.6 - 20.4)
Middle East and North Africa	39 (1.0 %)	9 (1.9 %)	23.1 (21.8 - 24.4)
Sub-Saharan Africa	20 (0.5 %)	0 (0.0 %)	0.0 (0.0 - 16.1)
Americas	21 (0.6 %)	1 (0.2 %)	4.8 (4.1 - 5.5)
Neighbourhood variables			
IRSD Scores ((Mean (SD))	940.5 (82.1)	934.1(88.3)	
IRSD			

Q1 (Highest disadvantage)	1752 (45.9 %)	229 (49.5 %)	13.1 (12.0 - 14.2)
Q2	943 (24.7 %)	120 (25.9 %)	12.7 (11.6 - 13.8)
Q3	620 (16.2 %)	75 (16.2 %)	12.1 (11.1 - 13.1)
Q4	362 (9.5 %)	34 (7.3 %)	9.4 (8.5 - 10.3)
Q5 (Lowest disadvantage)	139 (3.6 %)	7 (1.5 %)	5.1 (4.4 - 5.8)
Area level crime (Mean (SD)	831.4 (615.5)	833.9 (557.2)	
Area level crime (crime/1000)			
Q1 (Highest crime)	1900 (49.8 %)	270 (58.3 %)	14.2 (13.1 - 15.3)
Q2	847 (22.2 %)	105 (22.7 %)	12.4 (11.4 - 13.5)
Q3	655 (17.2 %)	62 (1.6 %)	9.5 (8.6 - 10.4)
Q4	317 (8.3 %)	20 (0.5 %)	6.3 (5.5 - 7.1)
Q5 (Lowest crime)	97 (2.5 %)	6 (0.2 %)	6.2 (5.4 - 7.0)
Access to Health care (Mean (SD)	2.2 (3.6)	2.2 (3.6)	
Access to Health care (index)			
Q1 (Highest access)	833 (21.8 %)	114 (24.6 %)	13.7 (12.6 - 14.8)
Q2	968 (25.4 %)	98 (21.2 %)	10.1 (9.1 - 11.1)
Q3	1339 (35.1 %)	160 (34.6 %)	11.9 (10.9 - 12.9)
Q4	592 (15.5 %)	82 (17.7 %)	13.9 (12.8 - 15.0)
Q5 (Lowest access)	84 (2.2 %)	9 (1.9 %)	10.7 (9.7 - 11.7)
Green space Availability (%) (Mean (SD)	14.3 (18.0)	13.1 (17.5)	
Availability of green spaces (%)			
Q1(Highest availability)	93 (2.4 %)	10 (2.2 %)	10.8 (9.8 - 11.8)
Q2	341 (8.9 %)	37 (8.0 %)	10.9 (9.9 - 11.9)
Q3	688 (18.0 %)	82 (17.7 %)	12.0 (11.0 - 13.3)
Q4	742(19.4 %)	82 (17.7 %)	11.05 (10.5 - 12.6)
Q5 (Lowest availability)	1952 (51.2 %)	252 (54.4 %)	12.9 (11.1 - 13.1)

Neighbourhood Obesity (Mean (SD)	17.9 (3.8)	18.0 (3.8)	
Neighbourhood Obesity (%)			
Q1 (Highest Obesity)	1444 (37.8 %)	175 (37.8 %)	12.1 (11.1 - 13.1)
Q2	974 (25.5 %)	118 (25.5 %)	12.1 (11.1 - 13.1)
Q3	873 (24.0 %)	100 (22.4 %)	11.5 (10.4 - 12.5)
Q4	446 (10.6 %)	64 (13.0 %)	14.3 (13.2 - 15.4)
Q5 (Lowest Obesity)	79 (2.1 %)	6 (1.3 %)	7.6 (6.8 - 8.4)
Fast food Availability (Median (SD)	9.20 (8.1)	10.0 (9.8)	
Fast food availability (no /1000)			
Available (> 0)	3157 (82.7 %)	380 (82.1 %)	12.0 (10.8 - 13.0)
Not available (0)	659 (17.3 %)	83 (17.9 %)	12.6 (11.6 - 13.7)

The median age of the SMI-T2D comorbidity subgroup was 59 years (range = 18 - 92 years). The gender distribution was approximately equal with females accounting for 52.9 % of the population. A higher proportion of SMI-T2D comorbidity was observed in adults over 65 years of age. With regards to country of birth, a higher percentage of SMI-T2D comorbidity was observed for individuals with SMI born in Middle East and North Africa (23.1%) followed by Eastern and Central Europe (23.2%) and Western Europe (21.2%). The prevalence SMI-T2D comorbidity in the most disadvantaged IRSD quintile (Q1) was 13.1% (n = 229) and that in the least disadvantaged quintile (Q5) was 5.1% (n = 7). While comparing the SMI diagnosis, SMI-T2D comorbidity was found to be higher in individuals with major depression followed by individuals with schizophrenia (Fig 3.2)

Figure 3. 2 : SMI diagnosis and prevalence of SMI-T2D comorbidity



Relative risk calculations

Relative risk of SMI-T2D comorbidity was calculated as a ratio of observed to expected counts for each of the 167 suburbs in the Illawarra Shoalhaven.

$$\mathbf{RR_i} = \frac{\mathbf{O_i}}{\mathbf{E_i}} \quad \textbf{(1)}$$

Where RR_i is the relative risk for i^{th} region, O_i is the number of observed SMI-T2D comorbidity counts for region i and E_i is the expected number of SMI-T2D comorbidity counts in region i.

The expected number of cases for each neighbourhood was calculated by means of indirect standardisation. Age-sex stratified population in each suburb was multiplied by

the age-sex stratified prevalence across the entire study area. Expected counts were calculated separately for males and females aged 18 - 44, 45 - 65 and 65+years. The calculated expected counts were then aggregated within suburbs to create a total denominator for the relative risk. Neighbourhoods with expected counts of zero (n = 5) were merged with the neighbouring suburbs with similar socioeconomic features for further analysis. Large variances were observed for SMI-T2D relative risks due to sparse comorbidity counts and the heterogeneous population density in the study area (see Chapter 4).

Geographic analysis

Spatial autocorrelation

Spatial autocorrelation measures the level to which the value of a variable at a certain geographic location relates to the same value in the neighbouring locations [37]. Global Moran's I, the most commonly used measure of spatial autocorrelation, was used to investigate spatial autocorrelation in the raw relative risk estimates [38]. Moran's I statistic can range between -1 and +1, with a value of zero indicating complete spatial randomness. A positive Moran's I value indicates positive spatial autocorrelation; and a negative value indicates a negative spatial autocorrelation [39]. Moran's I index was calculated using the formula below [39]. For an observation at location i, z_i is the attribute deviation of the feature xi from its mean $\bar{X}$, w_{ij} is the spatial weights, S_o is the sum of all spatial weights and n is the number of observations. Spatial weights are used to define and quantify the spatial relationships that exists among neighbourhood features [20].

$$\mathbf{I} = \frac{\sum_i \sum_j w_{ij} z_i . z_j / S_0}{\sum_i z_i^2 / n} \quad \textbf{(2)}$$

In this study, GeoDa software was employed to construct the spatial weight matrix, and to compute Global Moran's I [39]. This thesis used a queen contiguity spatial weights matrix, which is the spatial neighbouring criterion based on border and vertices sharing [40]. For example, in the above formula (3), consider i and j as two neighbouring units. If they are adjacent units, the value of w_{ij} will be one and if these two units share no border or point, the value of w_{ij} will be zero.

Statistical significance of the observed pattern is drawn based on the z score and the p values. Moran's I statistics is based on the null hypothesis of spatial randomness. A permutation based computational approach is used to calculate a reference distribution by randomly permuting the observed values over the locations. This reference distribution is then utilised to calculate a pseudo p value given by [41]

$$p = \frac{R+1}{M+1} \quad (3)$$

Where R is the number of times the computed Moran's I from the permuted data sets and M is the number of permutations, which in this analysis was set at 9999. When p value computed is greater than 0.05, the null hypothesis is accepted suggesting that data values are randomly distributed spatially. When the p value is less than 0.05 and the z score is negative, the null hypothesis is rejected suggesting that high and/or low values are dispersed geographically. Similarly, when z score is positive and p value is less than 0.05, the randomness assumption is again rejected, suggesting the spatial clustering of high and/or low values [42].

Empirical Bayes smoothing

Empirical Bayes smoothing approach was followed to improve the precision of the raw relative risk rates by shrinking and stabilising the rates towards the global mean of the

whole study region [43]. The technique involves constructing a weighted average between the crude rate for each suburb with weights proportional to the underlying population at risk. EB estimate for the relative risk in location i was given by [41, 43]

$$\mathbf{RR_{EB} = w_i\, r_i + (1 - w_i)\theta} \tag{4}$$

Weights (w_i) in the above equation is expressed as

$$\mathbf{w_i} = \frac{\boldsymbol{\sigma^2}}{(\boldsymbol{\sigma^2} + \frac{\boldsymbol{\mu}}{\mathbf{P_i}})} \tag{4.1}$$

Where P_i is the population at risk in area i , r_i is the raw relative risk rate and μ and σ^2 are the mean and variance estimated from the data as below

$$\boldsymbol{\mu} = \frac{\sum_{i=1}^{i=n} \mathbf{O_i}}{\sum_{i=1}^{i=n} \mathbf{P_i}} \tag{4.2}$$

$$\boldsymbol{\sigma^2} = \frac{\sum_{i=1}^{i=n} \mathbf{P_i}\,(\mathbf{r_i} - \boldsymbol{\mu})^2}{\sum_{i=1}^{i=n} \mathbf{P_i}} - \frac{\boldsymbol{\mu}}{\sum_{i=1}^{i=n} \mathbf{P_i}} \tag{4.3}$$

Empirical Bayes smoothing was carried out in this thesis using GeoDa [39]. The data from GeoDa was then visualised using ArcGIS version 10.5 [20].

Local indicator of spatial association (LISA)

Local Indicators of Spatial Association (LISA) or Local Moran's I is widely used in health research to identify the location of spatial clusters [44]. In this thesis, LISA was used to identify significant high rate and low rate clusters of SMI-T2D comorbidity. The spatial clusters identified by the local Moran's I can be divided into four types: high-high (high risk areas surrounded by other areas of significantly higher rates), high-low (high risk areas surrounded by low risk areas), low-high (low risk areas surrounded by high risk

areas), low-low (low risk areas surrounded by other low risk areas) [39, 44]. LISA statistic is explained by the following formula [41].

$$\textbf{Local Moran's I} = \mathbf{c}.\ (\mathbf{x_i} - \mathbf{\bar{X}}) \sum_j \mathbf{w_{ij}} (\mathbf{x_j} - \mathbf{\bar{X}}) \qquad \textbf{(5)}$$

Where, c is a constant based on the estimation of the variance when applied to each geographical unit; w_{ij} is the spatial weight matrix ; and $(x_i - \bar{X})$ and $(x_j - \bar{X})$ are the deviations from the mean for the i^{th} and j^{th} neighbourhood unit. Local Moran's I statistics was computed in this thesis using GeoDa software [39]. The spatial weights were provided using queens first order contiguity matrix. The information was then exported to Arc GIS for mapping [20]. The computation of LISA statistics is similar to global Moran's I, however permutations are carried out for each observation and a p value is generated for each location which can be used to assess significance. Spatial clusters are identified by combining the significance information along with the location of each observation in the Moran Scatterplot [39].

In chapter 4, bivariate LISA statistics was also computed to compare the geographic convergence of SMI and general diabetes (Gen-DM) in the Illawarra-Shoalhaven. The LISA bivariate statistic indicates how observations of a variable (SMI) in a certain suburb are associated with the observations of a different variable (Diabetes) in the adjacent suburb. In this case, high-high clusters will indicate coincident areas of high rates of SMI and Gen-DM and low-low clusters will be the areas of coincident low rates of SMI and Gen-DM.

An important consideration needed with LISA statistics is the selection of critical p value to reflect the desired Type 1 error rate. Due to the computational permutation process, LISA statistics suffer from the issue of multiple comparisons [41]. Assigning significance based on traditional p value choice of 0.05 is not meaningful and is likely to lead to many

false positives [41]. In order to overcome this issue, the Benjamini Hochberg Correction was applied to control for false discovery rates in both univariate and bivariate LISA analysis [39]. In this method, p values are sorted in increasing order and a new false rate discovery (FDR) variable which equals $i \times {}^{\alpha}/_{n}$ is created. In the formula, 'i' is the sequence number of the sorted observations, α is the target p-value (0.05) and 'n' is the number of observations [41]. Observations are considered significant if p values are ≤ FDR value. For example, in this study α is 0.05 and n is 167 (number of suburbs), the minimum p-value to be considered significant would be $\alpha\ /n$ = 0.0003.

Spatial scan statistics

Kulldorff's spatial scan statistic [45], implemented in SaTScan, was also used in this study to test for the presence of spatial clusters and to identify their locations [46]. This was used along with LISA statistics to complement the findings and to provide more informative results [47]. The statistic tests the null hypothesis that the risk of SMI-T2D comorbidity is same in all suburbs. The method uses a circular window of variable radii that gradually moves across the study area using a user defined maximum percentage of population at risk and noting the number of observed and expected observations inside the window at each location [46]. For each window, scan statistics tests the null hypothesis against the alternate hypothesis of elevated risk of SMI-T2D comorbidity within, compared to outside of the window [46]. The likelihood function of a specific window, under Poisson assumption is proportional to [48]

$$\left(\frac{n}{\mu}\right)^{2} \left(\frac{N-n}{N-\mu}\right)^{N-n} I(n > \mu) \quad \textbf{(6)}$$

Where N is equal to the total number of SMI-T2D comorbidity in the study area, n is the comorbidity counts within the window and μ is the expected number of comorbidities

within the window. I is an indicator function which is equal to 1 when the window has more comorbidity counts than expected under the null hypothesis and 0 otherwise. For fixed values of N and μ, the likelihood increases with increase in 'n'. The likelihood function is maximised over all the windows to identify the most likely comorbidity cluster and the likelihood ratio of this window is used as the maximum likelihood ratio test statistic [48]. The p values are obtained by repeating the same analytic exercise on a large number (9999) of random replications using Monte Carlo simulation. The null hypothesis of spatial randomness is rejected when the simulated p value is less than or equal to 0.05. The relative risk (RR) is also calculated for each cluster along with the p value. The RR value is based on how much greater the risk is inside the window compared to outside [46]. Clusters that are non-overlapping were only investigated and identified. The SMI-T2D comorbidity counts in this analysis was assumed to be Poisson distributed [46] and the maximum population at risk in this analysis was set at a default maximum spatial cluster size of ≤ 50% [45].

A multivariate spatial scan [46] statistic was also incorporated in chapter 4 of this thesis to test the association between SMI and diabetes, and to map their associations at suburb level. Multivariate spatial scan determines the spatial clusters with higher and lower rates for both SMI and diabetes (Gen-DM) by simultaneously searching for and evaluating clusters within the two datasets. The likelihood ratio for each data set is summed up to identify the likelihood ratio for that particular scanning window [46]. In this study, the statistical significance of multivariable spatial scan was set at a significance level of 0.05 and was evaluated under the complete spatial randomness assumptions using 9999 Monte Carlo simulations [49].

Variance inflation factor

The Variance inflation factor (VIF) was computed to check for multicollinearity, which is the relatedness among neighbourhood predictor variables [50]. Multicollinearity can cause parameter estimates to have magnitudes and signs that are not concordant with expectations and can cause larger standard errors [51]. In some instances of multicollinearity, variables may show no statistical significance despite large predictor outcome correlations [52]. The VIF was computed using the formula

$$\mathbf{VIF_j} = \frac{\mathbf{1}}{\mathbf{R_J^2}} \quad \textbf{(7)}$$

R_J^2 in the equation is the multiple correlation coefficient of the predictor which gives the proportion of variance in the outcome associated with the j^{th} predictor. VIF greater than 10 is considered to indicate multicollinearity [53]. No evidence of multicollinearity was observed after assessing all the neighbourhood variables included in this thesis (VIF < 3) (Appendix B).

Multilevel logistic regression modelling

Multilevel regression modelling is a statistical technique used to analyse hierarchical data [54]. Hierarchical data refer to data variables collected at multiple levels, whereby lower level data variables are nested within variables collected at one or more higher levels. For instance, patients with myocardial infarction who are nested within the hospitals in which they are admitted. The major advantage of multilevel modelling over traditional regression methods is that it allows researchers to model predictor variables at different levels [55]. This allows for realistic modelling of relationships and helps reduce errors in drawing inferences subject to ecological or atomistic fallacies [55, 56]. Moreover, multilevel models are capable of dealing with clustering in hierarchical data. For example,

the patients admitted in the same hospital may have related disease outcomes as they are subjected to the same hospital environment. Treating clustered data as independent entities may result in the underestimation of standard errors there by increasing Type 1 error [57].

In this study, multilevel logistic regression models accounting for clustering at the suburb level was used to model the presence or absence of SMI-T2D comorbidity. The data structure consisted of two levels: individuals (level 1) clustered with in suburbs (level 2). Intercepts were allowed to vary randomly across clusters by introducing cluster specific random effects. The model analysed is specified as below

$$\mathbf{logit}\left(\mathbf{Y_{ij}}\right) = \alpha_0 + \alpha_{0j} + \alpha_1 x_{1ij} + \cdots + \alpha_k x_{kij} + \beta_1 z_{1j} + \cdots + \beta_m z_{mj} \qquad (8)$$

Where Y_{ij} is the binary response variable measured on i^{th} person and j^{th} cluster, x_{iij} through x_{kij} denote the k explanatory variables measured on this person (for example age, and sex) , z_{1j} through z_{mj} denotes the m predictor variable measured on the j^{th} cluster(for example, neighbourhood socioeconomic disadvantage) and α_{0j} is the cluster-specific random effects.

A series of multilevel logistic regression models were fitted for the purpose of this thesis. First, an empty model was fitted (Model 1) which only included suburb level random effect. This allowed the identification of unadjusted contextual effects on SMI-T2D comorbidity. Thereafter, individual level factors were added (age, gender, country of birth) to the model (Model 2), followed by neighbourhood socio economic disadvantage (Model 3) and other neighbourhood level characteristics (Model 4).

In chapter 6, separate multilevel models were run for each of the neighbourhood variables to identify the specific associations between these neighbourhood features and SMI-T2D comorbidity. The covariates used in this analysis were age, sex, country of birth and

neighbourhood socioeconomic disadvantage. All neighbourhood level and individual level interactions were also examined in chapter 6. Models were estimated using maximum likelihood method with Laplace approximation [58]. Likelihood ratio tests were used to determine the goodness of fit [59]. All multilevel analysis was undertaken in R version 3.5, using the lme4 package [36]. The statistical significance was set at $p<0.05$. The R codes for the analysis are presented in Appendix C.

The fitted multilevel models had convergence issues initially. In order to overcome this, several trouble shooting procedures were carried out, such as checking for singularity, lowering convergence tolerances and testing different optimizers. Using optimizer 'bobyqa' for both phases instead of the default procedure of using 'bobyqa' for first phase and 'Nelder-Mead' for second phase rectified the convergence failure issues in this analysis.

Measures of area level variance and clustering

Intra class correlation (ICC)

Intra class correlation (ICC) can be interpreted as the proportion of total variance in the individual outcome that is attributable to between neighbourhood variations [60]. ICC can range between 0 and 1, with 0 representing completely independent observations and an ICC of 1 representing no cluster level variations. In multilevel logistic regression, the individual level variance and neighbourhood level variance are not comparable due to the difference in their scale (area level variance is on a logistic scale and individual level variance is on probability scale) [61]. In this study we used latent variable method in which individual level variance is converted from probability scale to logistic scale. On this basis ICC is specified as below [61]

$$\mathbf{ICC} = \frac{\mathbf{V_A}}{(\mathbf{V_A}+\mathbf{V_1})} \quad \textbf{(9)}$$

Where V_A is the area level variance and V_1 corresponds to the individual level variance

Median odds ratio (MOR)

Median Odds Ratio (MOR) was computed in this study to convert area level variance into an odds ratio scale. MOR is defined as the median value of odds ratio between the highest risk and the lowest risk neighbourhood when randomly picking out two analysis units [62]. In this study MOR describes the extent to which the probability of having SMI-T2D comorbidity is determined by neighbourhood. The MOR is interpreted as the increased risk in comorbidity when an individual moves to a suburb of higher risk [62]. MOR closer to 1 implies no variation between areas whereas larger MOR values indicate considerable inter neighbourhood variation [62]. MOR was computed using the following formula specified by Merlo et al and Austin et al. [60, 61]

$$\mathbf{MOR} = \mathbf{exp}\left(\sqrt{(\mathbf{2} \times \mathbf{V_A})} \times \mathbf{0.6745}\right) \quad \textbf{(10)}$$

$$\approx \mathbf{exp}\left(\mathbf{0.95}\sqrt{\mathbf{V_A}}\right. \quad \textbf{(10.1)}$$

Proportional change in variance (PCV)

Proportional change in variance (PCV) was also reported to show how much of the residual variance was explained by the addition of explanatory variables in each of the models. PCV was calculated as [63]

$$\mathbf{PCV} = \frac{(\mathbf{V_A} - \mathbf{V_B})}{\mathbf{V_A}} \times \mathbf{100} \quad \textbf{(11)}$$

Where V_A is the residual variance of the initial model and V_B is the residual variance of model with added terms.

Ethics

The University of Wollongong and Illawarra Shoalhaven Local Health District Human Research Ethics Committee approved the research described in this thesis (protocol number 2017/428). The Human research ethics committee determined that there was no requirement to obtain informed consent because individuals could not be identified from the data used for the conduct of this study. Use of information that may reveal patient or community identity, such as naming the neighbourhoods were however restricted.

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Chapter 4

Exploring the geography of serious mental illness and type 2 diabetes comorbidity in the Illawarra-Shoalhaven, Australia (2010 -2017).

A journal article based on the findings from this chapter is published in the PLOSONE Journal. The study as it appears in print is available in the appendix (Appendix D).

Reference

Walsan, R., Mayne, D.J., Pai, N., Feng, X., & Bonney, A., 2019, '*Exploring the geography of serious mental illness and type 2 diabetes comorbidity in Illawarra—Shoalhaven, Australia (2010 -2017)',* PLOS ONE, 14 (12), p 1-13.

Authorship details

Walsan (70 %) - Conceptualisation, analysis, interpretation, drafting and reviewing final manuscript

Bonney (10%) - Supervision, interpretation, reviewing final manuscript

Mayne (10 %) - Supervision, analysis, interpretation, reviewing final manuscript

Pai (5 %) - Supervision, interpretation, reviewing final manuscript

Feng (5 %) - Supervision, interpretation, reviewing final manuscript

Contribution to the thesis

Responding to the aim 1 of the thesis, this chapter describes the geography of SMI-T2D comorbidity in the Illawarra-Shoalhaven. This study also aimed to determine the geographic convergence if any, between the comorbidity and the single diagnosis of SMI

and diabetes. This study was crucial for deciding the feasibility of the subsequent studies. Before examining neighbourhood level associations with SMI-T2D comorbidity, it was important to ascertain the presence of neighbourhood level variations in the distribution of SMI-T2D comorbidity.

Abstract

Objectives.

The primary aim of this study was to describe the geography of serious mental illness (SMI)-type 2 diabetes comorbidity (T2D) in the Illawarra-Shoalhaven region of NSW, Australia. The Secondary objective was to determine the geographic concordance if any, between the comorbidity and the single diagnosis of SMI and diabetes.

Methods

Spatial analytical techniques were applied to clinical data to explore the above objectives. The geographic variation in comorbidity was determined by Moran's I at the global level and the local clusters of significance were determined by Local Moran's I and spatial scan statistic. Choropleth hotspot maps and spatial scan statistics were generated to assess the geographic convergence of SMI, diabetes and their comorbidity. Additionally, we used bivariate LISA (Local Indicators of Spatial Association) and multivariate spatial scan to identify coincident areas with higher rates of both SMI and T2D.

Results

The study identified significant geographic variation in the distribution of SMI-T2D comorbidity in the Illawarra-Shoalhaven. Consistently higher burden of comorbidity was observed in some urban suburbs surrounding the major metropolitan city. Comparison of comorbidity hotspots with the hotspots of single diagnosis SMI and T2D further revealed a geographic concordance of high-risk areas again in the urban areas outside the major metropolitan city.

Conclusion

The identified comorbidity hotspots in our study may serve as a basis for future prioritisation and targeted interventions. Further investigation is required to determine whether contextual environmental factors, such as neighbourhood socioeconomic disadvantage, may be explanatory.

Implications for public health

Ours is the first study to explore the geographic variations in the distribution of SMI and T2D comorbidity. Findings highlight the importance of considering the role of neighbourhood environments in influencing the T2D risk in people with SMI.

Introduction

Research has established that type 2 diabetes (T2D) often co-occurs with serious mental illness (SMI) such as schizophrenia, bipolar disorder and major depression [1]. People with SMI have 2 - 4 times higher risk of developing T2D compared with the general population, which translates into an average reduction of 15 - 20 years in their life expectancies [2, 3]. In contrast, several lines of evidence also suggest that a diagnosis of T2D can increase the risk of mental disorders such as depression [4]. For people with SMI, a comorbid diabetic diagnosis not only confers a higher cardiovascular risk and increased risk of premature mortality, but is also associated with greater cognitive decline, worse prognosis, increased hospitalisations, greater number of emergency department visits, non-adherence to treatments, higher healthcare utilisation costs and decreased quality of life for people experiencing mentally ill-health [3, 5-9].

Significant geographic inequalities have been reported in the distribution of both severe mental illness and T2D [10-18]. However, to the best of our knowledge, geographic variations in their comorbidity have not been previously explored. A recent systematic literature review reported a paucity of research literature investigating the association between neighbourhoods and SMI-T2D comorbidity [19]. Moreover, in recent years, there has been increased interest in addressing comorbid conditions concurrently rather than as separate diseases and an integrated management approach is now considered superior over a single focus approach [20]. Exploring neighbourhood variations in the co-occurrence and clustering of SMI-T2D may help us to better understand the overlapping prevalence of these two chronic diseases and to propose novel hypotheses regarding the neighbourhood level factors that might influence the co-occurrence. Describing the geography may also assist public health authorities to cost-effectively target local

resources and preventive interventions to reduce the regional disparities and public health burden imposed by the comorbidity.

Accordingly, the purpose of this study was to examine the neighbourhood level geographic variations in SMI-T2D comorbidity, in an Australian community using cross-sectional, routinely collected clinical data. We also aimed to determine the geographic concordance, if any, between the comorbidity and the single diagnosis of SMI and T2D.

Research Design and Methods

Study area and population

This cross-sectional study was carried out in the Illawarra and Shoalhaven regions of New South Wales, Australia, which had an estimated resident population of 368,604 people at the time of the 2011 Australian Census of Population and Housing [21]. Serious mental illness and diabetes comorbidity data for the period of 2010 to 2017 were obtained from the Illawarra Health Information Platform (IHIP), which is a research partnership established between Illawarra Shoalhaven Local Health District (ISLHD) and University of Wollongong for the purpose of providing ISLHD health service data to researchers. Community-derived diabetes data (without reference to comorbidities), were retrieved from the Southern IML Research (SIMLR) study database for the period of 2010 to 2014. SIMLR is a longitudinal, community derived near-census database consisting of routinely collected pathology results for residents 18 years and over in the Illawarra-Shoalhaven [14]. All the data used in this study were deidentified prior to extraction, consistent with the requirements of the Privacy Act 1988 (Cth) and Health Records and Information Privacy Act 2002 (NSW). Residential suburbs were the smallest geographical units at which health service data were available and were used as the spatial units of analysis. Information on the population of the region by age groups and gender was obtained from

the 2011 Australian Census of population and housing [21]. To display and analyse the geographic distribution of SMI, T2D and their comorbidity, a base map of the Australian suburbs 2011 digital boundaries from Australian Bureau of Statistics was used. This study was approved by The University of Wollongong and Illawarra Shoalhaven Local Health District Human Research Ethics Committee (protocol number 2017/428).

Study sample

Serious mental illness in our study was defined as a primary or secondary diagnosis of SMI from the inpatient records of ISLHD. Data extraction was carried out by means of International Classification of Diseases (ICD) 10 codes (Table 4.1). Comorbidity was defined as having a T2D stay diagnosis code (ICD code E11) in people with serious mental illness recorded in the ISLHD data. Comorbidity details were extracted as either present or absent along with each of the SMI records. The community derived diabetes sample, consisted of individuals with at least one HbA1c test between 2010 and 2014 and an HbA1c result ≥ 6.5 % or plasma glucose levels ≥7.0mmol/L within 12 months of an HbA1c test, consistent with thresholds used in the Australian National Health Measures Survey [22]. Data analysis was restricted to individuals 18 years and over.

Table 4. 1 : SMI diagnosis groups and ICD 10 codes included in the study

Diagnosis	**ICD 10 codes**
Schizophrenia	F20
Other non-affective psychosis	F22 – F29
Bipolar disorder	F30, F31
Major depression	F32, F33
Other affective disorders	F34, F39

Statistical Analysis

We calculated the relative risk of SMI-T2D comorbidity for each of the 167 suburbs in the Illawarra-Shoalhaven region by computing the ratio of observed to the expected counts. The expected number of cases was calculated by indirect standardisation and was obtained by multiplying the age-sex stratified population in each suburb by the age-sex stratified prevalence across the entire study area. Expected counts for males and females aged 18 - 34, 35 - 49, 50 - 64 and 65+ years were calculated separately and were then aggregated within suburbs to create an aggregated denominator for the relative risk. Data over the entire study period (2010 - 2017) were combined to ensure sufficient counts. The population profile of the study area had remained relatively similar during these time period [21]. Suburbs with expected counts of zero (n = 5) were merged with the neighbouring suburbs for further analysis. Large variance in relative risks was observed due to sparse comorbidity counts and the heterogeneous population density in the area. To address this issue, relative risk data were smoothed using the Empirical Bayes smoothing technique recommended by Anselin and Koschinsky to shrink and stabilise the rates towards the global mean of the whole study region [23].

Global Moran's I was used to investigate spatial autocorrelation or clustering in the raw estimates [24]. Moran's I statistic ranges between -1 and 1, with a value of zero indicating complete spatial randomness; a positive value indicating positive spatial autocorrelation; and a negative value indicating negative spatial autocorrelation [24]. Local Indicator of Spatial Association (LISA) and spatial scan statistics were used to identify the location of comorbidity clusters. These two spatial analytical techniques were adopted simultaneously to complement the findings and to provide more intuitive results [25]. LISA, often known as Local Moran's I, was used to detect the significant clusters of higher and lower relative risks of comorbidity [24]. High-high clusters are areas of

significantly high rates surrounded by other areas of significantly higher rates, and low-low clusters represents areas with lower risks surrounded by other areas of lower values [26, 27] .

Spatial scan statistics works by imposing circular scanning windows of varying radii, which gradually moves over the study area evaluating the likelihood ratios of all potential clusters using a user defined maximum percentage of population at risk [28], which in this analysis was set at a default maximum spatial cluster size of ≤ 50% [29]. We employed a purely spatial retrospective scan using the discrete Poisson model, whereby the number of events is assumed to be Poisson distributed [28] . The input data for this model consisted of the observed and the expected comorbidity counts. The 'no geographic overlap' criterion was used to report the clusters.

In order to compare the geographic concordance of SMI-T2D comorbidity with the single diagnosis of SMI and diabetes in the general population (Gen-DM), relative risk maps, LISA maps and spatial scan statistics were generated for SMI and Gen-DM following the same procedures as the comorbidity map. Additionally, we used bivariate LISA [26, 27] and multivariate spatial scan [28] statistics to test the association between SMI and Gen-DM and to map their associations at suburb level. The LISA bivariate statistic indicates how observations of a variable (SMI) in a certain suburb are associated with the observations of a different variable (Gen-DM) in the adjacent suburb. In our case, high-high clusters will indicate coincident areas of high rates of SMI and Gen-DM and low-low clusters will be the areas of coincident low rates of SMI and Gen-DM. Multivariate spatial scan identifies spatial clusters with higher and lower rates for both SMI and Gen-DM by simultaneously searching for and evaluating clusters within the two datasets. The likelihood ratio for each data set is summed up to determine the likelihood ratio for that particular window [28].

The statistical significance of Global Moran's I, Local Moran's I, Spatial scan and bivariate LISA were evaluated under the complete spatial randomness assumptions using 9999 Monte Carlo simulations and a significance level of 0.05 [30]. Benjamini Hochberg correction was applied to control for false discovery rates in LISA and Bivariate LISA statistics [27].

Software: We used GeoDa [27] for Empirical Bayes Smoothing and spatial analysis, SaTScan for univariate and multivariate spatial scan statistics [28], R for descriptive analysis [31] and ArcGIS 10.5 for mapping [32].

Results

Sample description

A total of 4165 unduplicated records were extracted with an SMI diagnosis between 1 January 2010 and 31 December 2017. Individuals residing outside the Illawarra-Shoalhaven area (n = 50) and records with no suburb information (n = 283) were excluded from our analysis (n = 341, 8.2 %) resulting in a final SMI sample of 3824 people. Of these, 463 (12.1 %) had a T2D comorbidity. The community derived diabetes sample for the region consisted of 13142 unique individuals. The distribution of SMI, diabetes and their comorbidity in the Illawarra-Shoalhaven is described in Table 4.1. The median age of the comorbidity subgroup was 58 years (range = 18 - 92 years). The gender distribution was approximately equal with females accounting for 52.9% of the sample. Higher comorbidity prevalence was observed in older adults above 50 years of age.

Spatial distribution of SMI -T2D comorbidity

The geographic distribution of smoothed relative risks for SMI-T2D comorbidity in the Illawarra-Shoalhaven is depicted in Fig 4.1. Moran's I revealed a positive global spatial autocorrelation for SMI - T2D relative risk (Moran's I = 0.1155, p = 0.0361) indicating

that suburbs with similar SMI-T2D risk are clustered geographically. Fig 4.2 demonstrates the results of the application of LISA and spatial scan statistics to the SMI-T2D comorbidity risk by suburbs.

Table 4. 2 : Distribution of serious mental illness, type 2 diabetes and their comorbidity in the Illawarra-Shoalhaven (2010 - 2017)

Demographic characteristics	Serious mental illness	Diabetes	Serious mental illness -type 2 diabetes comorbidity
Total	**3824**	**13142**	**463**
Sex			
Male n (%)	1977 (51.7)	7248 (55.2)	218 (47.1)
Female n (%)	1847 (48.3)	5894 (44.8)	245 (52.9)
Age (Years)			
18 - 34 n (%)	1132 (29.6)	189 (1.4)	27 (5.8)
35 - 49 n (%)	1220 (31.8)	733 (5.6)	108 (23.3)
50 - 64 n (%)	820 (21.4)	3294 (25.1)	150 (32.4)
65 and over n (%)	652 (17.1)	8926 (67.9)	178 (38.4)

Figure 4. 1 : Smoothed relative risk of SMI-T2D comorbidity in the Illawarra-Shoalhaven (2010 - 2017)

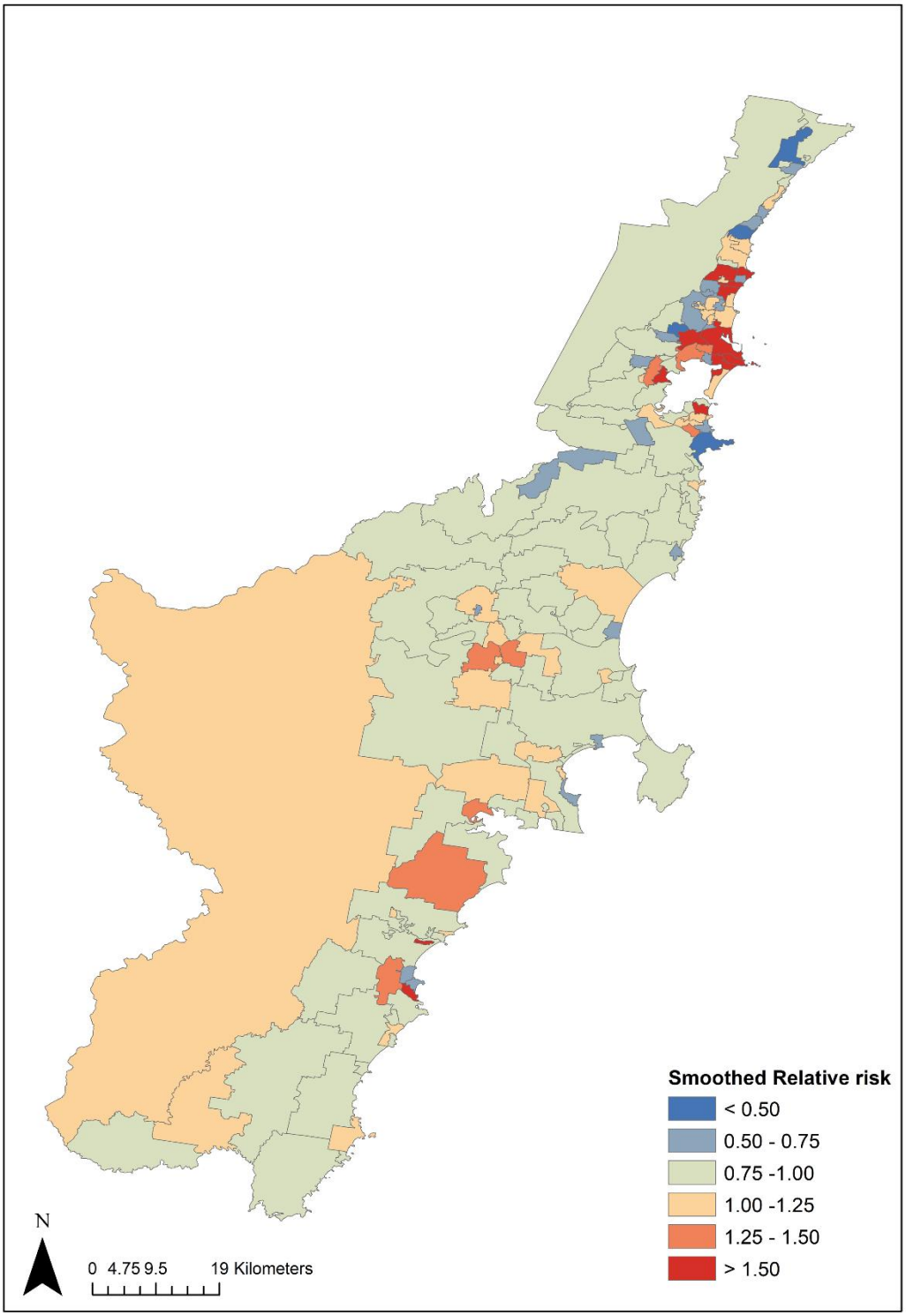
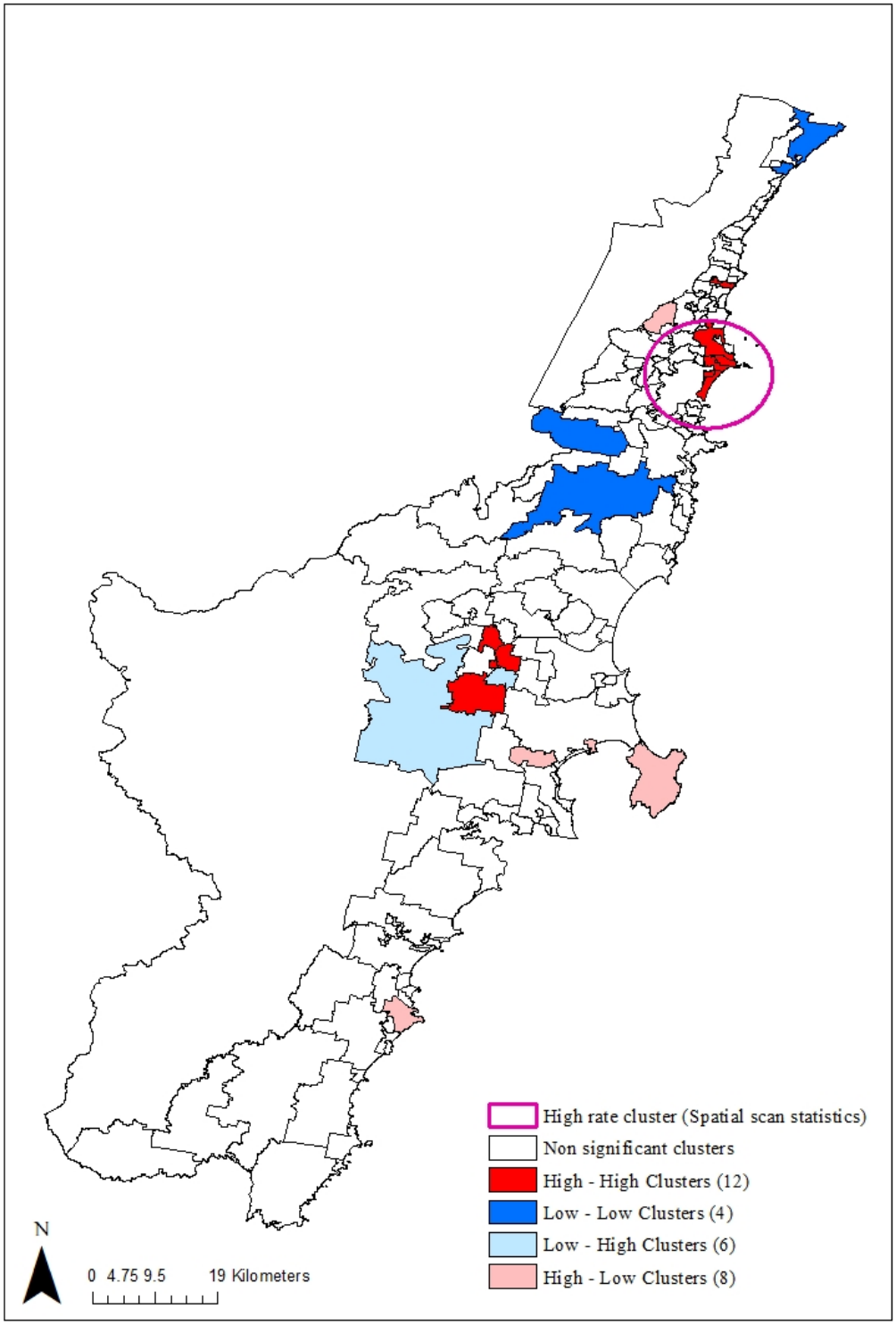


Figure 4. 2: Local Moran's I and spatial scan statistics calculated for SMI-T2D comorbidity in the Illawarra-Shoalhaven (2010 -2017)



LISA analysis identified twelve (12) significant high-high clusters (hotspots) and four (4) low-low clusters (cold spots), that became non-significant after correcting for multiple comparisons using the Benjamini Hochberg FDR procedure. However, there was a strong correspondence between uncorrected LISA hotspots and spatial scan cluster locations as shown in figure 4.2. The spatial scan statistics using a maximum cluster size of ≤50% of total population identified one significant high rate cluster of SMI-T2D comorbidity in the suburbs south of the major metropolitan city centre (north east of study area) (Fig 4.2). As ethical approval for this study was conditional on not disclosing suburb names/locations, the major city centre is not highlighted in the figure. The high rate cluster identified comprised of 23 urban suburbs and had a relative risk of 1.80 ($p < 0.001$). The number of observed comorbidity cases in this cluster was 110, compared to 68 expected cases. The identified high rate cluster contained 14.2 % of the total population in the Illawarra-Shoalhaven. No significant low rate clusters were detected by spatial scan. Six urban suburbs south of major metropolitan city were identified as high-risk areas for SMI-T2D comorbidity as they consistently appeared in both LISA and spatial scan statistics as a high rate cluster.

Geographic concordance of SMI, T2D and their comorbidity

In order to compare the geographic concordance of SMI-T2D comorbidity with the SMI and diabetes risk in the Illawarra-Shoalhaven, smoothed relative risk maps, LISA maps and spatial scan statistics were generated for SMI, Gen-DM and SMI-T2D comorbidity (Fig 4.3). For SMI, we identified 6 high-high clusters, 10 low-low clusters, 4 low-high clusters and 8 high-low clusters. For Gen-DM the high-high, low-low, low-high and high-low clusters identified were 6, 12, 2 and 5 respectively. Both LISA and spatial scan statistics (Table 4.3) consistently identified a convergence of hotspots (high-high clusters)

for SMI, T2D and their comorbidity in four urban suburbs south of the major metropolitan centre, which was previously identified as a comorbidity hotspot.

Figure 4.4 shows the result of bivariate LISA analysis and multivariate spatial scan for SMI and diabetes in the Illawarra-Shoalhaven. Five high-high clusters indicating suburbs of higher SMI risk surrounded by neighbourhoods of higher diabetes risk were observed in the southern urban areas. The analysis also revealed 7 low-low clusters in the central part of study region. Similar to LISA clusters, application of multiple comparison correction to these results didn't yield any significant results. Multivariate spatial scan analysis with a maximum spatial cluster size of up to 50% identified one high rate cluster for both SMI and Gen-DM comprising of 4 suburbs with a relative risk of 1.63 (log likelihood ratio 178.8 , p <0.001).

Table 4. 3 : Significant spatial scan clusters of SMI, Diabetes (general population) and SMI-T2D comorbidity (Illawarra-Shoalhaven 2010 - 2017)

Diagnosis	Cluster Type	No. of suburbs	Observed count	Expected count	Relative risk	Log likelihood	P value
SMI	High	24	1350	1056.13	1.43	53.54	<0.001
	High	12	222	152.37	1.49	14.58	<0.001
	Low	16	248	404.99	0.59	38.89	<0.001
	Low	3	1	26.21	0.038	22.02	<0.001
	Low	5	31	60.43	0.094	14.53	<0.001
SMI-T2D Comor-bidity	High	23	163	102.97	1.89	20.02	<0.001
Gen-DM	High	4	917	577.09	1.63	89.40	<0.001
	High	5	1157	967.84	1.21	18.86	<0.001
	Low	14	1076	1555.69	0.66	92.80	<0.001
	Low	12	570	732.79	0.77	20.65	<0.001

Figure 4. 3 : Geographic distribution and significant hotspots for SMI, Diabetes and SMI-T2D comorbidity in the Illawarra-Shoalhaven (2010 - 2017)

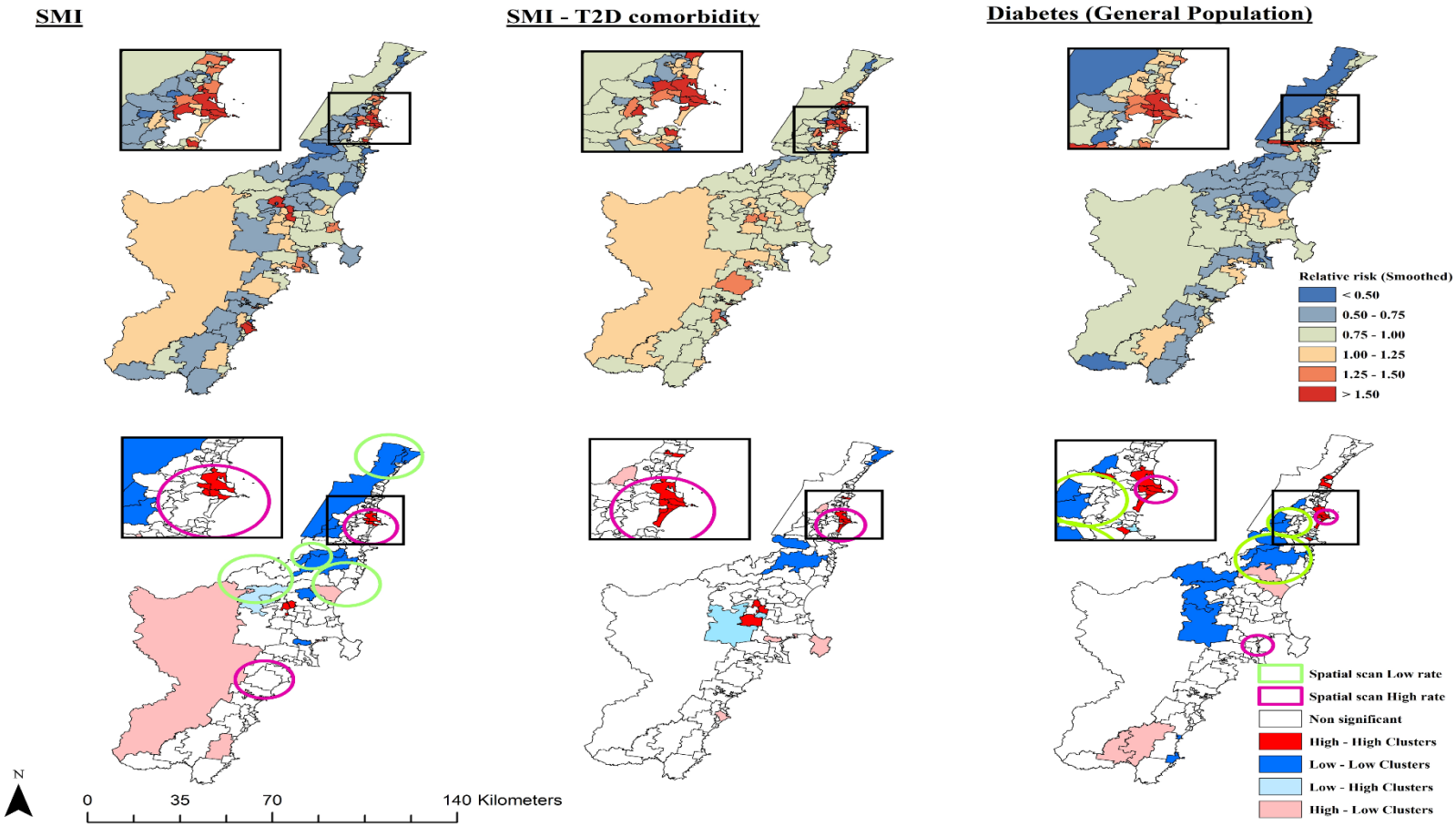
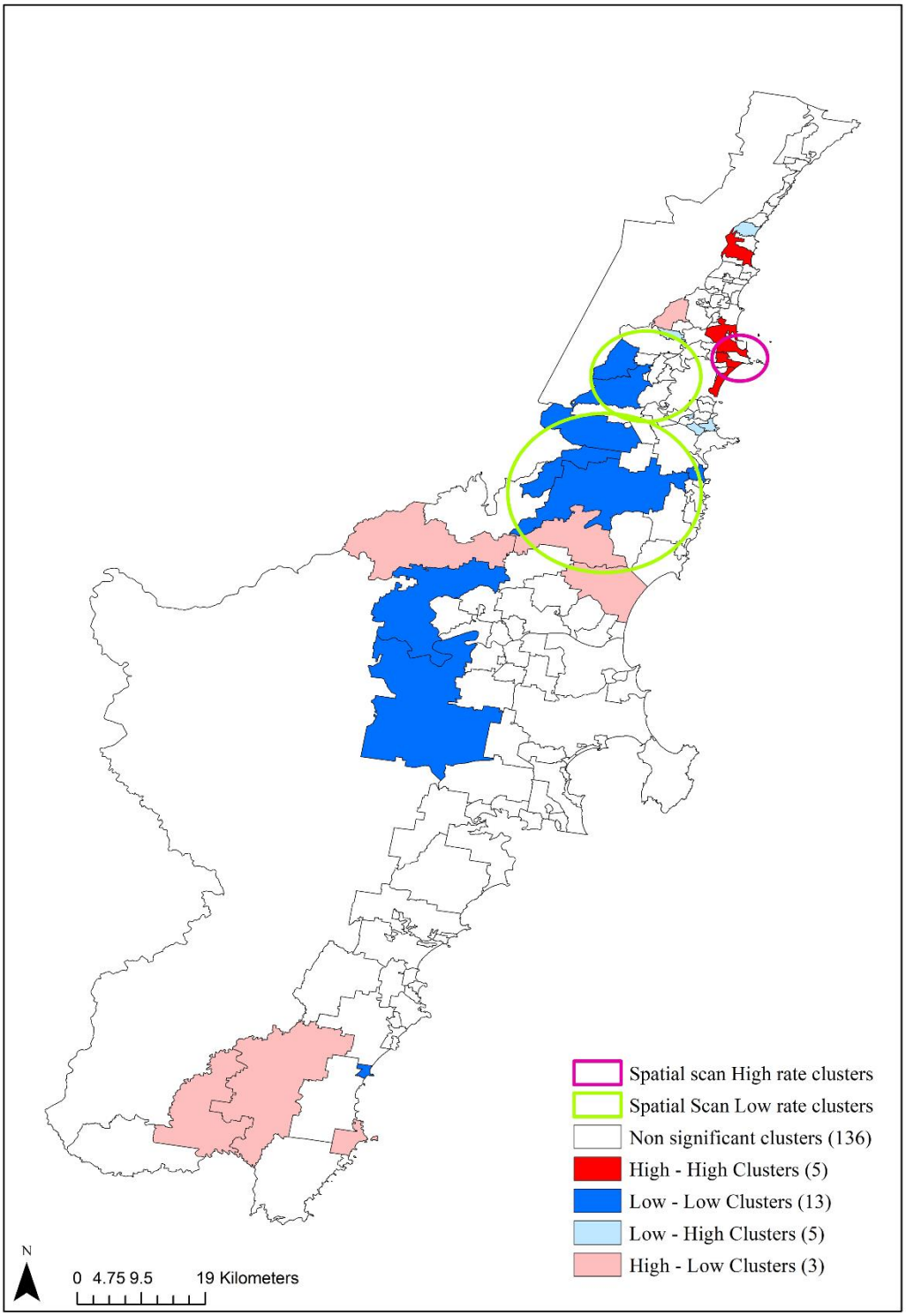


Figure 4. 4 : Bivariate LISA based spatial clusters showing the local association between SMI and diabetes in the Illawarra-Shoalhaven (2010 - 2017)



Discussion

The present study identified geographic variations in the distribution of SMI-T2D comorbidity in the Illawarra-Shoalhaven. The spatial dependence of comorbidity was confirmed by the global test for spatial autocorrelation (Moran's I). In other words, suburbs with higher comorbidity risk tend to locate closer than we would expect at random. Conversely, suburbs with lower comorbidity risk also tend to cluster together geographically. Using local indicators of spatial association (LISA and spatial scan statistics), we were able to identify a consistently higher burden of comorbidity in six urban suburbs south of the metropolitan city. These suburbs are relatively homogeneous in terms of their population density and socioeconomic environments. Comparison of comorbidity hotspots with the hotspots of single diagnosis SMI and diabetes further revealed a geographic concordance of high-risk areas in four urban regions of the main metropolitan area. These findings suggest that the population in some urban suburbs are challenged by SMI, T2D and their comorbidity and appropriate prevention and management initiatives should be targeted accordingly. This study has also demonstrated the potential usefulness of combining spatial analytical methods and clinical data information to inform health service commissioning and geographically target needs-based preventive interventions.

We observed that both LISA and bivariate LISA clusters became non-significant after correcting for multiple comparisons using Benjamini Hochberg procedure. Even though Benjamini Hochberg correction is a less conservative method compared to other false discovery correction procedures, there can still be substantial loss of power (constraining the type I error rate at the expense of an increasing type II error rate) when dealing with bigger datasets [27]. This loss of power could have contributed to our null results.

Correspondence between uncorrected LISA hotspot clusters and spatial scan clusters indicate that our results remain interesting.

This is the first study to explore the geographic variations in the distribution of SMI and T2D comorbidity. Lack of evidence in this important area of public health was highlighted in a recent systematic literature review [19]. Previous research has, however, established significant geographic inequalities and urban clustering in the distribution of both SMI and type 2 diabetes [13-18]. In this study, we were able to demonstrate that this relationship holds true for their comorbidity as well. From a health service research and policy perspective, describing the geography of coexisting diseases together might prove more useful in aiding decisions on the allocation of resources and integrated interventions. Findings from this study will also create opportunities for further exploratory hypothesis testing, using spatial clustering as a framework. One commonly hypothesised and plausible contributory exposure is neighbourhood socioeconomic disadvantage. Disadvantaged neighbourhoods often expose mentally ill persons to greater psychosocial stress, or act as a proxy for adverse health behaviours such as unhealthy eating, lack of physical activity and obesity, which have been shown to be associated with increased T2D risk [17, 33, 34]. Thus, identification and exploration of these neighbourhood features that might influence SMI-T2D comorbidity will be an important next step for enhancing our understanding of the geography of comorbidity and will be addressed in future research.

The overall aim of our study was to generate information that could be useful to guide health service policies and preventive interventions aimed at reducing the burden of T2D comorbidity in people with serious mental illness. We have identified hotspots of SMI, T2D and their comorbidity in some urban regions of the Illawarra-Shoalhaven. Targeted

health care strategies focussed on these regions may possibly reduce the health inequality and public health burden imposed by SMI-T2D comorbidity.

The results from this study should be interpreted with respect to their limitations. Firstly, the serious mental illness and comorbidity data used in this study were sourced only from inpatient mental health records of ISLHD and did not consider outpatient and private practice records. Though this is supported by the data from the Australian National Surveys of Psychosis indicating that 45.6 - 62.9% of people with SMI reported ≥1 hospital admission for any reason in the previous 12 months [35], the results may not be generalisable to all individuals with SMI as only a specific cohort of patients from an institution was studied. It is reported that SMI population attending private clinics may be systematically different from those attending inpatient public health services with respect to their demographics, health literacy and disease severity [36] and this may have an effect on the external validity of this study findings. The second limitation is the cross-sectional study design that does not permit cause and effect conclusions. There is also a possibility of reverse causality, confounding bias, and unmeasured mediating and moderating factors and this may have overestimated the neighbourhood effects. We also note that there is a potential for temporal misalignment as 2011 census data were used as the reference population. This may have led to inferential bias although, a sensitivity analysis using 2016 census data did not alter the results significantly.

Conclusions

In this study we combined spatial analytical methods and clinical data to analyse the spatial distribution of SMI-T2D comorbidity in Illawarra-Shoalhaven. Our results revealed evidence of spatial variations in the distribution of SMI-T2D comorbidity. The high-risk clusters were mainly located in the urban areas. The findings from this study emphasise the geographic focus needed in these regions to reduce the T2D burden in SMI.

This study has also demonstrated the potential of spatial analytical methods in assessing and identifying spatial disparities in the comorbid disease risks so that preventive interventions and resources are appropriately targeted. Further investigation using multilevel analytical techniques is required to determine whether particular environmental factors such as neighbourhood socioeconomic disadvantage may be explanatory for these geographic variations in SMI-T2D comorbidity. Understanding the neighbourhood correlates will help us in developing evidence based holistic interventions, health care policies and potentially the design of healthier places to live.

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CHAPTER 5

Examining the association between neighbourhood socioeconomic disadvantage and type 2 diabetes comorbidity in serious mental illness

This chapter is a reproduction of the peer-reviewed journal article published in the International Journal of Environmental Research and Public Health's special edition titled 'Current Trends in Mental Health Research in Asia Pacific Region'. The study as it appears in the print is available in the appendix (Appendix E).

Reference

Walsan R, Mayne D J, Feng X, Pai N, Bonney A. Examining the Association between Neighbourhood Socioeconomic Disadvantage and Type 2 Diabetes Comorbidity in Serious Mental Illness. *International Journal of Environmental Research and Public Health*. 2019;16(20). doi:10.3390/ijerph16203905.

Authorship details

Walsan (70 %) - Conceptualisation, analysis, interpretation, drafting and reviewing final manuscript

Bonney (10%) - Supervision, interpretation, reviewing final manuscript

Mayne (10 %) - Supervision, analysis, interpretation, reviewing final manuscript

Pai (5 %) - Supervision, interpretation, reviewing final manuscript

Feng (5 %) - Supervision, interpretation, reviewing final manuscript

Contribution to the thesis

As the first study demonstrated significant geographic variations in the distribution of SMI-T2D comorbidity (SMI-T2D), this second study aimed to determine whether neighbourhood socioeconomic disadvantage is associated with these variations. A further objective of study 2 was to determine how much variance of SMI-T2D comorbidity between neighbourhoods was attributable to neighbourhood disadvantage. Multilevel logistic regression models accounting for neighbourhood level clustering were adopted to evaluate the adjusted association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity.

Abstract

Objectives: This study examined the association between neighbourhood socioeconomic disadvantage and serious mental illness (SMI)-type 2 diabetes (T2D) comorbidity in an Australian population using routinely collected clinical data. We hypothesised that neighbourhood socioeconomic disadvantage is positively associated with T2D comorbidity in SMI.

Method: Analysis considered 3816 individuals with a SMI living in the Illawarra and Shoalhaven regions of NSW, Australia, between 2010 and 2017. Multilevel logistic regression models accounting for suburb (neighbourhood) level clustering were used to assess the association between neighbourhood disadvantage and SMI-T2D comorbidity. Models were adjusted for age, sex and country of birth

Results: Compared with the most advantaged neighbourhoods, residents in the most disadvantaged neighbourhoods had 3.2 times greater odds of having SMI-T2D comorbidity even after controlling for confounding factors (OR 3.20, 95% CI 1.42 - 7.20). Analysis also revealed significant geographic variation in the distribution of SMI-T2D comorbidity in our sample (Median odds ratio = 1.35) Neighbourhood socioeconomic disadvantage accounted for approximately 17.3% of this geographic variation.

Conclusions: These findings indicate a potentially important role for geographically targeted initiatives designed to enhance prevention and management of SMI-T2D comorbidity in disadvantaged communities.

Introduction

Serious mental illness (SMI) is a term used to refer severe and persistent forms of mental disorders such as schizophrenia, bipolar disorder or major depression [1]. Individuals with SMI have 2 to 4 times increased risk of developing type 2 diabetes (T2D) compared with the general population which translates into a reduction of 15 - 20 years in their life expectancies [2-4]. A comorbid T2D diagnosis is also associated with other adverse consequences such as increased hospitalisations, greater number of emergency department visits, non-adherence to treatments, higher healthcare utilisation costs, higher risk of cognitive deficit, poor clinical outcomes and decreased quality of life for the mentally ill [2, 5-11].

People with SMI are more likely to live in disadvantaged neighbourhoods [12, 13] and the environment in these neighbourhoods may compound the experiences of psychosocial stress or promote engagement in adverse health behaviours (e.g. unhealthy eating and physical inactivity) and weight gain, all of which contribute to T2D risk [12, 14, 15]. A number of studies have found that the prevalence of SMI and T2D are both separately higher in more socioeconomically disadvantaged neighbourhoods [13, 16-19]. However, research to date has not adequately examined the association between area level disadvantage and SMI-T2D comorbidity. A recent systematic review [20] examining this relationship identified only a single study demonstrating a tentative association between the neighbourhood level disadvantage and T2D comorbidity in mental illness [21]. The aforementioned study, however, focused entirely on major depression and did not consider other forms of SMI such as schizophrenia or bipolar disorder. Hence additional research on the association between neighbourhood disadvantage and SMI-T2D comorbidity is warranted, given the paucity of evidence available and the plausibility of an association. We have recently reported significant geographic variations in the

distribution of SMI-T2D comorbidity suggesting the need to explore the role of neighbourhood level disadvantage in explaining this variation [22].

Establishing strong evidence of the relationship between neighbourhood disadvantage and SMI-T2D comorbidity is an important step in advancing our understanding of the T2D comorbidity in SMI and the possible associations neighbourhood environments might have with this comorbidity. Moreover, population-based prevention strategies that shift the risk distribution of an entire population in a favourable direction are considered more effective and sustainable than individual based approaches in reducing the disease burden [23]. Understanding these associations may also be useful for health policy makers to develop integrated interventions and to provide greater diversity of care needed to optimally manage the complex needs associated with comorbidity.

The aim of this study was to investigate the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity in an Australian population using routinely collected clinical data. We hypothesised that greater socioeconomic disadvantage would be associated with increased T2D comorbidity in SMI. A further objective was to determine how much variance of SMI-T2D comorbidity between neighbourhoods was attributable to neighbourhood socioeconomic disadvantage.

Materials and Methods

Study design and sample

We used a cross-sectional, multilevel study design to examine the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity. The study area comprised the Illawarra and Shoalhaven regions of NSW, Australia, which had an estimated resident population of 368,604 people at the time of 2011 Australian Census of Population and Housing [24]. The region has a mix of rural and urban influences and is

comprised of the local government areas of Kiama, Shellharbour, Shoalhaven and Wollongong. The socioeconomic profile of the study area as described by region's socioeconomic index scores are comparable to that of NSW and Australian average [25, 26]. The data analysed in this study covered the period 01 January 2010 to 31 December 2017 and were retrieved from Illawarra Health Information Platform (IHIP). The IHIP is a research partnership established between Illawarra Shoalhaven Local Health District (ISLHD) and University of Wollongong for the purpose of providing ISLHD health service data to clinicians and researchers. Analysis was undertaken at the state suburb level (SSCs), which was the smallest geographic unit at which the health service data were available. State suburbs are the Australian Bureau of Statistics (ABS) approximation of suburbs gazetted by the Geographical Names Board of NSW [27]. The Illawarra-Shoalhaven region comprised of 167 suburbs with an average land area of 36.56 km^2 and 2207 residents each in 2011 [24].

This study was approved by University of Wollongong and Illawarra Shoalhaven Local Health District Human Research Ethics Committee (protocol number 2017/428).

Measures

Data extraction was carried out using International Classification of Diseases (ICD) version 10 codes and was restricted to adults 18 years and over. We defined SMI as having a primary or secondary diagnosis of schizophrenia (F20), other non-affective psychosis (F22 - F29), bipolar disorder (F30, F31), major depression (F32, F33) or other affective disorders (F34, F39) in the inpatient records of ISLHD. Diabetes comorbidity, the outcome of interest, was defined as having a T2D diagnosis (E11) in people with SMI and was extracted as either present or absent along with each of the SMI records. The analytical sample was formed by excluding individuals residing outside the Illawarra and

Shoalhaven regions (n = 50) and individuals with no suburb (n = 283) or country of birth information (n = 8). The final SMI sample consisted of 3816 individuals of whom 463 (12.09 %) had a T2D comorbidity.

Neighbourhood socioeconomic disadvantage was operationalised for suburbs using the Index of Relative Socioeconomic Disadvantage (IRSD) from the 2011 Socioeconomic Indexes for Area Census product [26]. An IRSD score reflects the aggregate level of socioeconomic disadvantage measured on the basis of 17 variables including education, income, occupation, unemployment, housing type, overcrowding and English proficiency. For this study, IRSD scores for Illawarra and Shoalhaven suburbs were divided into quintiles of neighbourhood disadvantage with Quintile one (Q1) denoting the 20% most disadvantaged suburbs in Illawarra-Shoalhaven and Quintile five (Q5) the least disadvantaged 20%. Global Moran's I revealed a significant spatial dependence for neighbourhood socio economic disadvantage quintiles (Moran's I = 0.443673, p = <0.0001) indicating that suburbs with similar relative neighbourhood disadvantage are clustered geographically [28]. Quintiles were then assigned to individuals based on their suburb of residence at their most recent admission before 31 December 2017.

Individual level variables included in the analysis were sex, age at most recent admission and the country of birth. Age was categorized into three groups: young adults between 18 - 44 years; middle-aged between 45 - 65 years; and older adults above 65 years. This categorisation was in accordance with sociological and epidemiological life course framework of different stages of life [29]. Sex was grouped as male or female. Country of birth data were aggregated based on the *Standard Australian Classification of Countries* produced by the Australian Bureau of Statistics [30].

Statistical analysis

Multilevel logistic regression models accounting for suburb level clustering were used to assess the association between neighbourhood disadvantage and SMI-T2D comorbidity. The data structure consisted of two levels with individuals (level 1) nested within suburbs (level 2). A series of models were fit as follows: model 1 included only suburb level random effect; model 2 added individual level factors (age, gender, country of birth) to model 1; and model 3 added neighbourhood level IRSD quintiles to model 2. Interactions between individual variables and neighbourhood disadvantage were also considered in modelling to investigate any cross-level effect modification of the association by individual level factors. Models were estimated using maximum likelihood method with Laplace approximation [31]. Intra class correlation (ICC) and Median Odds ratios (MOR) were calculated for each model to assess how much of the variance in comorbidity could potentially be attributed to neighbourhoods [31, 32]. ICC informs us regarding the variance between areas [33]. The MOR is interpreted as the increased risk in comorbidity when an individual moves to a suburb of higher disadvantage [34]. MOR closer to 1 implies little variation between areas whereas larger MOR values indicate considerable variation between areas [34]. We also reported proportional change in variance (PCV) to show how much of the residual variance was explained by the additional explanatory variables in each of the models. ICC, MOR and PCV were derived from model outputs following the methods specified by Merlo et al and Austin et al [32, 33]. Likelihood ratio tests were used to determine the goodness of fit of the models. All statistical analysis was completed using R version 3.5 [35]. Statistical significance in this analysis was set at $p<0.05$

Results

The descriptive characteristics of study population are given in Table 5.1. SMI-T2D comorbidity was present in 13.3% of females and 11.1% of males with an SMI diagnosis. The age group with highest proportion of comorbidity was 65+ (27.73%). With regards to country of birth, a higher percentage of T2D comorbidity was observed for SMI individuals born in Middle East and North Africa (23.1%), Eastern and Central Europe (23.2%) and Western Europe (21.2%). The SMI-T2D comorbidity prevalence in the most disadvantaged IRSD quintile (Q1) was 13.1% (n = 229) and that in the least disadvantaged quintile (Q5) was 5.1% (n = 7).

Table 5. 1 : Characteristics of study population variables

Variables	**Individuals with SMI n= 3816**	**Individuals with SMI-T2D comorbidity n = 463**	**% of individuals with SMI who also have comorbidity (95% Cl)**
Individual variables			
Gender			
Female	1848 (48%)	245 (53%)	13.3 (11.8 - 14.9)
Male	1968 (52%)	218 (47%)	11.1 (9.7 - 12.5)
Age, years (Mean (SD))	43.6 (18.5)	58.8 (15.7)	
Age, years			
18 – 44	1961 (51%)	92 (20%)	4.7 (03.8 - 05.7)
45 – 65	1213 (32%)	193 (42%)	15.9 (13.9 - 18.0)
65+	642 (17%)	178 (38%)	27.7 (24.3 - 31.2)
Country of birth			
Australia	3104 (81%)	339 (73%)	10.9 (9.9 - 12.1)
Oceania excluding Australia	74 (2%)	12 (3%)	16.2 (9.5 - 26.2)
UK & Ireland	212 (6%)	35 (8%)	16.5 (12.1 - 22.1)
Western Europe	137 (4%)	29 (6%)	21.2 (15.2 - 28.8)

Eastern and central Europe	125 (3%)	29 (6%)	23.2 (16.7 - 31.3)
North East Asia	17 (0%)	0 (0%)	0.0 (0 - 18.4)
South East Asia	51 (1%)	6 (1%)	11.8 (5.5 - 23.4)
Central and South Asia	16 (0%)	3 (1%)	18.8 (6.6 - 43.0)
Middle East and North Africa	39 (1%)	9 (2%)	23.1 (12.7 - 38.3)
Sub-Saharan Africa	20 (1%)	0 (0%)	0.0 (0 - 16.1)
Americas	21 (1%)	1 (0%)	4.8 (0.9 - 22.7)
Neighbourhood level variables			
IRSD as quintiles			
Q1(Highest)	1752 (46 %)	229 (49%)	13.1 (11.6 - 14.7)
Q2	943 (25 %)	120 (26%)	12.7 (10.7 - 14.9)
Q3	620 (16 %)	75 (16%)	12.1 (9.8 - 14.9)
Q4	362 (10 %)	34 (7%)	9.4 (6.8 - 12.8)
Q5 (Lowest)	139 (4 %)	7 (2%)	5.1 (2.5 - 10.0)

IRSD=Index of Relative Socioeconomic Disadvantage

Table 5.2 presents the results of multilevel logistic regression analysis. Model 1 provides the estimate of between area variation in SMI-T2D comorbidity without any explanatory variables. The MOR for model 1 was 1.35, indicating some level of geographic variation in the distribution of SMI-T2D comorbidity in our sample. Moreover, the ICC for model 1 was 0.029, showing that 2.9% of the variance in comorbidity was attributable to between neighbourhood differences. The addition of individual level variables in model 2 accounted for 25.5% of between area variance and addition of IRSD in model 3 accounted for an additional 17.3% and reduced the MOR to 1.25. After inclusion of individual and neighbourhood variables, the ICC decreased from 2.9% to 1.7%.

Results for individual level variables in Model 2 indicate that age was significantly associated with SMI-T2D comorbidity. Older individuals with SMI have significantly

higher odds of having T2D comorbidity compared with younger individuals. Model 3 showed a significant association between higher levels of neighbourhood disadvantage and diabetes comorbidity in SMI after controlling for age, gender and country of birth. Living in a neighbourhood with highest socioeconomic disadvantage was associated with 3 times increased odds of having SMI-T2D comorbidity compared with the least disadvantage neighbourhood (OR 3.20, 95% CI 1.42 - 7.20 for Q1 vs Q5). Including two-way interaction terms in Model 3 indicated no evidence of effect modification of the association between SMI-T2D comorbidity and IRSD by age (χ^2_{LRT} = 14.16, DF = 8, p = 0.077), gender (χ^2_{LRT} = 1.45, DF = 4, p = 0.835) or country of birth (χ^2_{LRT} = 30.68, DF = 38, p = 0.794).

Table 5. 2 : The association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity using multilevel analysis (Illawarra-Shoalhaven, 2010 – 2017)

Variable	**Model 1**	**Model 2**	**Model 3**
		OR (95% Cl)	**OR (95% Cl)**
Individual variables			
Gender		*p = 0.658*	*p = 0.687*
Female		1.00	1.00
Male		0.95 (0.78 - 1.17)	0.96 (0.78 - 1.17)
Age		*p < 0.05*	*p < 0.05*
18 - 44		1.00	
45–65		3.79 (2.91 - 4.93)	3.78 (2.90 - 4.92)
65+		7.68 (5.77 - 10.23)	7.82 (5.87 - 10.42)
Country of birth		*p = 0.137*	*p = 0.149*
Australia		1.00	1.00
Oceania excluding Australia		1.57 (0.81 - 3.03)	1.53 (0.79 - 2.97)
UK & Ireland		0.84 (0.57 - 1.26)	0.88 (0.59 - 1.31)
Western Europe		0.99 (0.63 - 1.54)	0.97 (0.62 - 1.52)
Eastern and central Europe		1.30 (0.82 - 2.05)	1.30 (0.82 - 2.06)

South East Asia		1.30 (0.53 - 3.19)	1.30 (0.52 - 3.19)
Central and South Asia		2.03 (0.53 - 7.82)	2.13 (0.56 - 8.10)
Middle East and North Africa		1.84 (0.83 - 4.09)	1.87 (0.84 - 4.16)
Americas		0.42 (0.06 - 3.25)	0.41 (0.05 - 3.15)
Neighbourhood Variable			
IRSD quintiles			*p <0.05*
Q5 (Least disadvantaged)			1.00
Q4			1.87 (0.77 - 4.53)
Q3			2.67 (1.14 - 6.15)
Q2			2.92 (1.28 - 6.67)
Q1(Most disadvantaged)			3.20 (1.42 - 7.20)
Variance of random effects			
T^2	0.098	0.073	0.056
PCV	Ref	25.5%	42.9%
ICC	0.029	0.0217	0.017
MOR	1.347	1.293	1.252

OR: Odds Ratio, 95% Cl: 95% confidence interval, T^2 : Area level variance, PCV: Proportional change in Variance, ICC: Intra Class Correlation , MOR: Median Odds Ratio

Model 1: Null model with suburb level random effect

Model2: Model 1 + individual level factors

Model 3: Model 2+ neighbourhood level IRSD quintiles

Discussion

We found an independent positive association between neighbourhood disadvantage and SMI-T2D comorbidity after controlling for individual age, gender and country of birth. Neighbourhood socioeconomic disadvantage accounted for 17.3% of the between neighbourhood variation in SMI-T2D comorbidity. Among the individual level factors, age was independently associated with SMI-T2D comorbidity. Individual factors accounted for 25.5% of the between neighbourhood variation. Neither gender nor country of birth were associated with SMI-T2D comorbidity. Lower neighbourhood variance in

SMI-T2D comorbidity (ICC = 0.029) reported in our study does not preclude important neighbourhood level effects [36]. Misspecification of neighbourhoods, smaller group sizes and omission of a relevant level 1 variable may all have contributed to the under-estimation of neighbourhood variance [37]. All of these may have occurred in this study as these factors were constrained by the data available. Further research is hence required to confirm the findings. Low Intra class correlation (ICC) can coexist with important neighbourhood level fixed effects and several of these examples are available in public health where risk factors explain very little neighbourhood variance but are important predictors of health outcomes [37]. Additionally, Geoffrey Rose had pointed out that even small neighbourhood effects when aggregated at population scales can have a massive impact [23].

Ours appears to be one of the first studies to explore the association between area level disadvantage and SMI-T2D comorbidity. The only other study addressing this research question investigated major depression only and reported a positive but non-significant association between area level disadvantage and SMI-T2D comorbidity [21]. Our findings are, however, consistent with prior studies, which show significant neighbourhood level socioeconomic inequalities in the distribution of SMI [13, 17, 38] and T2D [18, 19, 39, 40] as independent conditions. In their systematic review, Mair et al identified 45 studies, of which 37 reported significant associations between neighbourhood characteristics and depression [41]. Similarly, the significant associations between neighbourhood environments and T2D risk was revealed in another systematic review by Dendup et al. [42].The findings of a positive significant association between SMI-T2D comorbidity and age and a non-significant association between SMI-T2D comorbidity and gender are consistent with previous reports in the literature [3, 43, 44].

The results from this study have policy implications for planning interventions and resourcing public health services. Our results indicate that efforts to reduce diabetic comorbidity in serious mental illness might benefit by focussing on individuals with SMI living in higher deprivation neighbourhoods. These results also have future research implications. Understanding why neighbourhood level disadvantage is associated with comorbidity is an important next step in addressing these inequities and in developing sustainable interventions and long-term solutions. There are several plausible explanations for increased SMI-T2D comorbidity in more disadvantaged neighbourhoods, over and above individual level factors. Neighbourhood-level features, such as green spaces, access to health care services, availability of fast food restaurants and area level crime may be differentially present in advantaged and disadvantaged neighbourhoods [45]. These may in turn act as a stimulus for chronic stress or adverse health behaviours such as unhealthy eating, lack of physical activity and obesity, which have been shown to be associated with increased T2D risk [12, 14, 15]. Further exploration of the mediating or confounding roles played by these contextual variables may improve our understanding of SMI-T2D comorbidity and the casual pathways linking them with the neighbourhood environments.

There are some limitations with our study. First, the cross-sectional study design does not allow us to draw cause-effect conclusions. Second, we used data sourced only from inpatient mental health records and did not consider outpatient and private practice records. However, the Australian National Surveys of Psychosis indicates that 45.6-62.9% of people with SMI reported ≥1 hospital admission for any reason in the previous 12 months [46], which should have provided a reasonable coverage given our eight year data collection period. In addition, we acknowledge the potential for temporal misalignment as 2011 relative disadvantage index scores were used in this analysis.

Nonetheless a weighted Kappa analysis between 2011 and 2016 disadvantage quintiles revealed a good agreement between the two (k = 0.796) indicating that the deprivation scores have remained relatively similar during these periods. Individual socioeconomic status, ethnicity, age at diagnosis and number of hospital admissions, were not included in this analysis due to the lack of data availability. This may have resulted in the overestimation of neighbourhood level effects. These results may be subjected to inferential bias as IRSD was allocated based on the most recent admission and hence residential mobility of individuals with SMI was not accounted for in this analysis. It was observed that the 95 % confidence intervals for the association between neighbourhood disadvantaged quintiles and SMI-T2D comorbidity overlapped indicating a weaker association than observed and should be regarded cautiously given the small sample sizes in the quintiles. Nonetheless, it should be noted that overlapping confidence intervals does not always imply that there is no statistical difference between the two groups [47]. Finally, we also acknowledge the potential for reverse causation as individuals with SMI may have moved to lower socioeconomic neighbourhoods.

Conclusions

Our results indicate that the people with SMI living in the most disadvantaged neighbourhoods are more likely than their counterparts in least disadvantaged neighbourhoods to report SMI-T2D comorbidity. These findings highlight the need to consider public health prevention strategies at both individual and neighbourhood level in order to reduce the public health burden imposed by comorbidity. The current study makes a significant contribution to the scant research literature available in this area of public health. Future research is needed to extend these findings and to consider how various neighbourhood contextual features may mediate the effect of neighbourhood socioeconomic disadvantage on SMI-T2D comorbidity.

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CHAPTER 6

Neighbourhood environment and type 2 diabetes comorbidity in serious mental illness

This chapter is a reproduction in full of the peer-reviewed journal article published in the Journal of Primary Care and Community Health'. The study as it appears in the print is available in the appendix (Appendix L).

Reference

Walsan R, Feng X, Mayne D J, Pai N, Bonney A. Neighborhood Environment and Type 2 Diabetes Comorbidity in Serious Mental Illness. Journal of Primary Care & Community Health. 2020. **11**: p. 2150132720924989. doi: https://doi.org/10.1177/21501327209249

Authorship details

Walsan (70 %) - Conceptualisation, analysis, interpretation, drafting and reviewing final manuscript

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Mayne (10 %) - Supervision, analysis, interpretation, reviewing final manuscript

Pai (5 %) - Supervision, interpretation, reviewing final manuscript

Feng (5 %) - Supervision, interpretation, reviewing final manuscript

Contribution to the thesis

The final study of this thesis examines the association between neighbourhood contextual features and T2D comorbidity in SMI. Study 2 revealed that individuals with SMI residing in the most disadvantaged neighbourhoods are more likely than their

counterparts in least disadvantaged neighbourhoods to report SMI-T2D comorbidity. Further exploration and quantification of the effect of specific neighbourhood level characteristics was undertaken in this next study to extend these findings and to advance our understanding of T2D comorbidity in SMI and the possible associations neighbourhood environments might have with this comorbidity.

Abstract

Aim

The aim of this study was to examine the association between neighbourhood characteristics and type 2 diabetes (T2D) comorbidity in serious mental illness (SMI). We investigated associations of neighbourhood level crime, accessibility to health care services, availability of green spaces, neighbourhood obesity, and fast food availability with SMI-T2D comorbidity.

Method

A series of multilevel logistic regression models accounting for neighbourhood level clustering were used to examine the associations between five neighbourhood variables and SMI-T2D comorbidity, sequentially adjusting for individual-level variables and neighbourhood-level socioeconomic disadvantage.

Results

Individuals with SMI residing in areas with higher crime rates per 1000 population had 2.5 times increased odds of reporting T2D comorbidity compared to the individuals with SMI residing in lower crime rate areas after controlling for individual and areal level factors (95% CI 0.91 - 6.74). There was no evidence of association between SMI-T2D comorbidity and other neighbourhood variables investigated.

Conclusion

Public health strategies to reduce SMI-T2D comorbidity might benefit by targeting on individuals with SMI living in high crime neighbourhoods. Future research incorporating longitudinal designs and/or mediation analysis are warranted to fully elucidate the mechanisms of association between neighbourhoods and SMI-T2D comorbidity.

Introduction

Research literature reports a median type 2 diabetes (T2D) prevalence rate of approximately 13% in populations with serious mental illnesses (SMI) such as schizophrenia, bipolar disorder or major depression [1]. This represents a two- to four-fold increase in risk compared with the general population [1,2]. Both SMI and T2D contribute significant individual and public health burdens when present independently and are the two leading causes of morbidity worldwide [3]. The comorbidity compounds this burden by worsening the outcomes for each condition [4]. Type 2 diabetes comorbidity in SMI is associated with several adverse consequences such as increased mortality; reduced life expectancy of up to 30 years; worse cognitive decline; poor clinical and functional outcomes; higher health care costs; and reduced quality of life for people with mental illness [2, 5, 6].

Neighbourhood characteristics have been extensively linked to traditional risk factors of T2D such as physical inactivity, poor quality diet, stress and obesity [7-11]. Some studies have also investigated more specific features of neighbourhood environments in relation to T2D risk. For example, reports from the Multiethnic Study of Atherosclerosis indicated that living in a neighbourhood with better resources for physical activity and healthy food was associated with lower prevalence of insulin resistance [10] and lower incidence of T2D [10, 12]. Sundquist et al. reported negative associations between neighbourhood built environmental features and T2D risk in a large sample of Swedish adults [13]. Studies from Australia have reported significantly lower incidence of T2D in greener neighbourhoods after controlling for sociodemographic factors [14, 15]. Neighbourhood social features such as safety and crime were also found to be associated with conditions related to diabetes such as obesity, reduced physical activity and psychological distress [16-18]. Neighbourhood characteristics have also been associated

with SMI [19-23]. Neighbourhood-level research on SMI has investigated a wide range of features including accessibility of health services [20], availability of green spaces [24], presence of tobacco and alcohol vendors [22], social capital and social disorder [23].

Few studies have explored the association between neighbourhood characteristics and T2D comorbidity in SMI, despite the public health burden and the plausibility of such associations [25]. Individuals with SMI are more likely to live in and be exposed to neighbourhood environments that exacerbate T2D risk such as higher concentration of fast food outlets, lack of health care resources, and unsafe environments due to their lower socio economic status [26, 27]. These contextual features may compound the experiences of psychosocial stress and encourage participation in adverse health behaviours such as unhealthy eating, physical inactivity and excess weight gain, all of which can contribute to T2D risk [17, 26]. We recently reported a statistically significant association between SMI-T2D comorbidity and neighbourhood-level socioeconomic disadvantage [28]. One of the plausible explanations for the higher SMI-T2D comorbidity risk in disadvantaged neighbourhoods may be the disproportionate availability of neighbourhood resources in more disadvantaged neighbourhoods as posited by the social determinants of health model [29]. For example, disadvantaged neighbourhoods may lack access to fresh produce and be dominated by fast food and convenience stores, making the latter the easily available food option [30]. Similarly, disadvantaged neighbourhoods might lack an environment conducive to physical activity [1]. Further exploration and identification of specific neighbourhood-level characteristics is required to advance our understanding of T2D comorbidity in SMI and the possible associations neighbourhood environments might have with this comorbidity. Understanding these associations may also help us to develop integrated policies or place-based interventions that promote healthier

environments to reduce the higher burden of T2D in individuals with SMI. There is however little evidence in the peer reviewed literature regarding the implementation and evaluation of such neighbourhood level integrated strategies on individuals with mental illness.

In this study we aimed to investigate the associations of neighbourhood environments with T2D comorbidity in individuals with SMI. A number of neighbourhood indicators of T2D risk previously identified in the literature were analysed. We specifically proposed to examine the association of five contextual neighbourhood factors with SMI-T2D comorbidity: (1) neighbourhood-level crime; (2) access to health care services; (3) availability of green spaces; (4) availability of fast food outlets; and (5) neighbourhood-level obesity [1, 7, 14, 17, 31-33].

Methodology

Study design and setting

This cross-sectional, multilevel study was conducted in Illawarra and Shoalhaven regions of New South Wales (NSW), Australia. The study site encompassed four local government areas of Kiama, Shellharbour, Shoalhaven and Wollongong, and had an estimated resident population of 368,604 people at the time of the 2011 Australian Census of Population and Housing [34]. State suburbs were used as proxies for neighbourhoods in this study as it was the smallest unit at which outcome data were available. State suburbs are the Australian Bureau of Statistics (ABS) approximation of suburbs gazetted by the Geographical Names Board of NSW [35]. The Illawarra-Shoalhaven region is comprised of 167 suburbs with an average population of 2207 residents in 2011 [34]. The University of Wollongong and Illawarra Shoalhaven Local Health District Human

Research Ethics Committee granted ethical approval for this study (protocol number 2017/428).

Individual-level data and the Outcome variable

The individual-level data utilized in this study were extracted from the Illawarra Health Information Platform (IHIP), a research partnership established between Illawarra Shoalhaven Local Health District (ISLHD) and University of Wollongong for providing de-identified ISLHD data to researchers. Data extraction was based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM), and covered the period from 2010 to 2017. Eligibility criteria required a primary or additional diagnosis of schizophrenia (F20), other non-affective psychosis (F22-F29), bipolar disorder (F30, F31), major depression (F32, F33) or other affective disorders (F34, F39) in the inpatient records of ISLHD. The outcome variable was SMI-T2D comorbidity, which was defined as having a T2D principal or stay diagnosis (E11) in people with SMI. Comorbidity details were extracted as either present or absent along with each record with an SMI diagnosis. We restricted our analysis to individuals with SMI who were 18 years and over. Individuals were excluded from the analysis if they lived outside the Illawarra - Shoalhaven (n = 50) or had missing information (n = 291). Consequently, the final sample comprised of 3816 individuals with a diagnosis of SMI, of whom 463 (12.3 %) had a T2D comorbidity.

Neighbourhood-level data

Our study focussed on five neighbourhood-level variables: (i) neighbourhood-level crime; (ii) access to health care services; (iii) neighbourhood-level obesity; (iv) availability of green spaces; and (v) availability of fast food outlets. The selection of explanatory variables included in this analysis was somewhat restricted by data

availability. Obesity was used as a contextual variable in this analysis as the information on individual-level obesity was not available for the study sample. Moreover, neighbourhood environments are reported to provide cues that support social norms defining individuals' healthy behaviours, which can be compromised in a higher obese neighbourhoods [36]. Hence the contextual effect of neighbourhood level obesity may be informative in determining the T2D risk in SMI.

Annual area-level crime counts were obtained from the NSW Bureau of Crime Statistics and Research for the period 2010 to 2017. Crime types considered were non-domestic violent assaults, homicides, malicious damage to properties, abduction and kidnapping, robbery and theft. Crime counts per neighbourhood were expressed as rates per 1000 people using estimated resident populations from the 2011 Australian Census of Population and Housing [34]. Health care services data were extracted from the National Health Service Directory (NHSD) available from the Australian Urban Research Infrastructure Network (AURIN) portal for the year 2016 [37]. To assess the availability of primary care, hospital and mental health services in Illawarra – Shoalhaven, we used the two-step floating catchment area method (2FSCA) that explicitly considers health care service supply and population demands and their interactions within a catchment [38]. In the first step, a 15 km distance catchment, corresponding to 30 minutes travel time [39] was placed around each health care service provider, and a provider to population ratio was computed and assigned to these health care facilities. The population of the entire suburb is included in these calculations if its centroid falls within a health service catchment. In the second step, a similar floating catchment was placed over the suburb centroid and all health care services falling in the area were identified. Accessibility was computed by summing all provider to population ratios contained

within the catchment. This method has been widely used in health care access research [39, 40].

Green space data were obtained from the AURIN portal and were available for 2018 only [41]. Data included green areas such as parks, reserves, national parks, conservation areas, forest reserves, recreational areas and other open spaces. We used the proportion of green space per suburb to assess the degree of exposure to green space. Neighbourhood level obesity was operationalised as percentage of population obese (BMI $\geq 30 kgm^{-2}$) in each neighbourhood [42]. Body mass index (BMI) data were extracted from Southern IML Research (SIMLR) Study database for the period 2010 to 2014. The SIMLR Study is a longitudinal, community-derived cohort comprising a near-census of data collected from individuals aged 18 years and over in Illawarra-Shoalhaven, while presenting for private pathology testing [43]. Finally, fast food data were sourced from Open Street Map [44], company websites and the Yellow Pages [45], and were extensively cross-checked and verified. We defined fast food outlets as service establishments that sell quickly prepared food with payment made prior to receiving food and with little table service [46]. A population-scaled measure of fast food density was derived as the number of outlets per 10,000 people, which was computed using the estimated resident populations from the 2011 Australian Census of Population and Housing [34].

All neighbourhood variables, except fast food density, were converted from their continuous form into quintiles, where Q1 represents the highest availability and Q5 the lowest. Fast food data were collapsed into a binary scale as there were many suburbs with zero outlets. The quintiles were then assigned to individual records based on their suburb of residence.

Covariates

Individual level covariates comprised age at most recent admission, gender and country of birth. Age was categorized as 18–44, 45–65 and 65+ years. Gender was categorised as male or female. Country of birth was grouped based on the Standard Australian Classification of Countries produced by the Australian Bureau of Statistics [47]. The Index of Relative Socioeconomic Disadvantage (IRSD) from the 2011 Socioeconomic Indexes for Areas product [47] was included in the analysis as a neighbourhood level covariate, as previous research had reported its association with SMI-T2D comorbidity [28]. The IRSD is an aggregate measure of the socioeconomic disadvantage for areas computed on the basis of 17 variables including education, income, occupation, unemployment, housing type, overcrowding and English proficiency. IRSD scores were classified into quintiles in this study.

Statistical analysis

Descriptive analysis was conducted, and variable distributions assessed. A two-stage modelling approach was used, whereby a series of single exposure multilevel models were run in the first stage followed by multi-exposure models in the second stage. Separate multilevel models were run in the first stage for each of the neighbourhood variables to identify the specific associations between neighbourhood features and SMI-T2D comorbidity. Three models were fit for each of the five neighbourhood variables and T2D comorbidity in SMI, accounting for neighbourhood level clustering. The first model was unadjusted; the second adjusted for individual level variables (age, gender, country of birth); and the third expanded model 2 with adjustment for neighbourhood level IRSD.

In the second stage, a series of multivariable random intercept logistic regression models were then calculated: first with no predictors; then with individual predictors only; and

finally, with both individual and neighbourhood level characteristics. This approach was used to estimate the intraclass correlation coefficient (ICC), and also to identify the potential confounding between various neighbourhood characteristics. The ICC is the proportion of variance in the outcome variable attributed to differences between individuals in different neighbourhoods as opposed to differences between individuals within the same neighbourhood and was calculated by the latent variable method [48, 49]. The proportion of the neighbourhood-level variance explained by different neighbourhood variables was also calculated [49]. The sensitivity of results to including neighbourhood-level obesity was evaluated by refitting the final model excluding this variable. All neighbourhood - and individual-level interactions were also examined to investigate potential cross-level effect modifications. Descriptive and multilevel analysis was completed using R version 3.5 [50] and the statistical significance was set at $p < 0.05$

Results

The study population consisted of 3816 individuals aged 18 years and over, of which 463 (12.3%) had a SMI-T2D comorbidity (Table 6.1). Individuals with comorbidity were mostly females (52.9 %), aged 65 years and older (38.4 %) and born in Australia (73.2 %). The distributions of neighbourhood variables are also given in Table 6.1. Variance inflation factors (VIF) were computed to ensure that multicollinearity did not bias the analysis [51]. Upon assessing all neighbourhood variables, none showed evidence of multicollinearity (VIF <3).

Table 6. 1 : Distribution of SMI-T2D comorbidity in Illawarra Shoalhaven (2010 – 2017)

Variables	Individuals with SMI n = 3816	Individuals with SMI+T2D n = 463	% comorbidity (95 % CI)
Individual variables			
Gender			
Female	1848(48.4 %)	245 (52.9 %)	13.3 (12.2–14.4)
Male	1968(51.6 %)	218 (47.1 %)	11.1 (10.1–12.1)
Age, years (Mean (SD))	43.6 (18.5 %)	58.8 (15.7 %)	
Age, years			
18–44	1961(51.4 %)	92 (19.9 %)	4.7 (4.0 -5.4)
45–65	1213 (31.8 %)	193 (41.7 %)	15.9 (14.7– 17.1)
65+	642 (16.8 %)	178 (38.4 %)	27.7 (26.3–29.1)
Country of birth			
Australia	3104 (81.3 %)	339 (73.2 %)	10.9 (9.9–11.9)
Oceania excluding Australia	74 (1.9 %)	12 (27.9 %)	16.2 (15.0–17.4)
UK & Ireland	212 (5.6 %)	35 (7.6 %)	16.5 (15.3–17.7)
Western Europe	137 (3.6 %)	29 (6.3 %)	21.2 (19.9–22.5)
Eastern and central Europe	125 (3.3 %)	29 (6.3 %)	23.2 (21.9–24.5)
North East Asia	17 (0.45 %)	0 (0.0 %)	0.0 (0.0–18.4)
South East Asia	51 (1.3 %)	6 (1.3 %)	11.8 (10.8–12.8)
Central and South Asia	16 (0.4 %)	3 (0.6 %)	18.8 (17.6–20.4)
Middle East and North Africa	39 (1.0 %)	9 (1.9 %)	23.1 (21.8–24.4)
Sub-Saharan Africa	20 (0.5 %)	0 (0.0 %)	0.0 (0.0–16.1)

Americas	21 (0.6 %)	1 (0.2 %)	4.8 (4.1–5.5)
Neighbourhood variables			
IRSD Scores (Mean (SD))	940.5 (82.1)	934.1(88.3)	
IRSD			
Q1 (Highest disadvantage)	1752 (45.9 %)	229 (49.5 %)	13.1 (12.0–14.2)
Q2	943 (24.7 %)	120 (25.9 %)	12.7 (11.6–13.8)
Q3	620 (16.2 %)	75 (16.2 %)	12.1 (11.1–13.1)
Q4	362 (9.5 %)	34 (7.3 %)	9.4 (8.5–10.3)
Q5 (Lowest disadvantage)	139 (3.6 %)	7 (1.5 %)	5.1 (4.4–5.8)
Area level crime (Mean (SD))	831.4 (615.5)	833.9 (557.2)	
Area level crime			
Q1 (Highest crime)	1900 (49.8 %)	270 (58.3 %)	14.2 (13.1–15.3)
Q2	847 (22.2 %)	105 (22.7 %)	12.4 (11.4–13.5)
Q3	655 (17.2 %)	62 (1.6 %)	9.5 (8.6–10.4)
Q4	317 (8.3 %)	20 (0.5 %)	6.3 (5.5–7.1)
Q5 (Lowest crime)	97 (2.5 %)	6 (0.2 %)	6.2 (5.4–7.0)
Access to Health care (Mean (SD))	2.2 (3.6)	2.2 (3.6)	
Access to Health care			
Q1 (Highest access)	833 (21.8 %)	114 (24.6 %)	13.7 (12.6–14.8)
Q2	968 (25.4 %)	98 (21.2 %)	10.1 (9.1–11.1)
Q3	1339 (35.1 %)	160 (34.6 %)	11.9 (10.9–12.9)
Q4	592 (15.5 %)	82 (17.7 %)	13.9 (12.8–15.0)
Q5 (Lowest access)	84 (2.2 %)	9 (1.9 %)	10.7 (9.7–11.7)

Green space Availability (Mean (SD))	14.3 (18.0)	13.1 (17.5)	
Availability of green spaces			
Q1(Highest availability)	93 (2.4 %)	10 (2.2 %)	10.8 (9.8–11.8)
Q2	341 (8.9 %)	37 (8.0 %)	10.9 (9.9–11.9)
Q3	688 (18.0 %)	82 (17.7 %)	12.0 (11.0–13.3)
Q4	742 (19.4 %)	82 (17.7 %)	11.05 (10.5–12.6)
Q5 (Lowest availability)	1952 (51.2 %)	252 (54.4 %)	12.9 (11.1–13.1)
Neighbourhood Obesity (Mean (SD))	17.9 (3.8)	18.0 (3.8)	
Neighbourhood Obesity			
Q1 (Highest Obesity)	1444 (37.8 %)	175 (37.8 %)	12.1 (11.1–13.1)
Q2	974 (25.5 %)	118 (25.5 %)	12.1 (11.1–13.1)
Q3	873 (24.0 %)	100 (22.4 %)	11.5 (10.4–12.5)
Q4	446 (10.6 %)	64 (13.0 %)	14.3 (13.2–15.4)
Q5 (Lowest Obesity)	79 (2.1 %)	6 (1.3 %)	7.6 (6.8–8.4)
Fast food Availability (Mean (SD))	9.3 (8.1)	10.0 (9.8)	
Fast food availability			
Available (> 0)	3157 (82.7 %)	380 (82.1 %)	12.0 (10.8–13.0)
Not available (0)	659 (17.3 %)	83 (17.9 %)	12.6 (11.6–13.7)

Table 6.2 presents single – exposure (stage 1) associations between neighbourhood features and SMI-T2D comorbidity. Only area level crime rates were significantly related to SMI-T2D comorbidity after adjusting for individual factors and neighbourhood level socioeconomic disadvantage (Table 6.2, Model 3): living in areas with a higher crime rate was associated with higher odds of SMI-T2D comorbidity compared to living neighbourhoods with a lower crime rate (OR 2.48, 95% CI 0.91 - 6.74). No significant associations were observed between health care access, neighbourhood obesity, green spaces or fast food availability and the odds of SMI-T2D comorbidity (Table 6.2, Model 3).

When all neighbourhood variables were included in multivariable models with individual-level covariates (see Table 6.3, Model 4), area level crime remained significantly associated with SMI-T2D comorbidity. The odds ratio for the highest crime quintile increased compared with the single exposure models and remained statistically significant (OR 2.78, 95 % CI 1.02 - 7.57, p = 0.002). The ICC for the null model was 0.029, indicating that 2.9 % of the variance in SMI-T2D comorbidity was attributable to between neighbourhood differences. Addition of all the neighbourhood features in model 4 (Table 6.3) accounted for 87.76% of between area variance and the ICC for this model was reduced to 0.004, indicating that the majority of residual variance in SMI-T2D risk was attributed to within neighbourhood rather than between neighbourhood differences. Sensitivity analysis excluding neighbourhood level obesity did not change the results substantially (Supplementary file 1). There was no evidence of interaction between individual and area level variables (Supplementary file 2).

Table 6. 2 : Results of single exposure multilevel logistic regression indicating the association between neighbourhood characteristics and SMI-T2D comorbidity in Illawarra- Shoalhaven (2010 – 2017)

Variable	Model 1		Model 2		Model 3	
	Odds ratio (95 % CI)	P value	Odds ratio (95 % CI)	P value	Odds ratio (95 % CI)	P value
Area level crime	1.17 (0.97–1.41)	0.002	1.19 (0.99–1.44)	0.013	1.02 (0.82–1.28)	0.032
Area level Crime						
Q1 (Highest crime)	2.90 (1.21–6.97)		3.08 (1.28–7.44)		2.48 (0.91–6.74)	
Q2	2.30 (0.94–5.60)		2.59 (1.06–6.35)		2.11 (0.77–5.76)	
Q3	1.59 (0.65–3.94)	<0.001	1.61 (0.65–3.99)	<0.001	1.27 (0.46–3.49)	0.001
Q4	1.00 (0.37–2.66)		1.17 (0.43–3.13)		1.02 (0.36–2.83)	
Q5 (Lowest crime)	1.00		1.00		1.00	
Access to health care	1.0 (0.89–1.12)	0.984	0.99 (0.88–1.11)	0.870	1.05 (0.94–1.19)	0.385
Access to Health care						
Q1 (Highest access)	1.34 (0.61–2.94)		1.46 (0.66–3.21)		1.68 (0.76–3.71)	
Q2	0.96 (0.43–2.11)		1.05 (0.47–2.33)	0.386	1.11 (0.47–2.33)	0.241
Q3	1.18 (0.54–2.57)		1.27 (0.58–2.78)		1.35 (0.62–2.96)	
Q4	1.39 (0.62–3.09)		1.42 (0.63–3.16)		1.39 (0.63–3.09)	
Q5 (Lowest access)	1.00		1.00		1.00	
Availability of green spaces	0.91 (0.81–1.03)	0.137	0.90 (0.79 -1.00)	0.064	0.94 (0.83–1.08)	0.378
Availability of green spaces						

Q1(Highest availability)	0.74 (0.36 -1.52)		0.72 (0.34–1.50)		1.08 (0.50–2.32)	
Q2	0.76 (0.50–1.18)		0.73 (0.47–1.12)		0.88 (0.56–1.37)	
Q3	0.82 (0.58–1.16)	0.318	0.81 (0.58–1.14)	0.285	1.02 (0.70–1.47)	0.511
Q4	0.71 (0.50–1.02)		0.73 (0.52–1.02)		0.76 (0.54–1.07)	
Q5 (Lowest availability)	1.00		1.00		1.00	
Neighbourhood Obesity	1.05 (0.93–1.19)	0.390	1.05 (0.93–1.19)	0.426	1.00 (0.99–1.00)	0.384
Neighbourhood Obesity						
Q1 (Highest Obesity)	1.85 (0.76–4.53)		1.65 (0.66–4.10)		1.19 (0.48–2.97)	
Q2	1.66 (0.67–4.10)		1.53 (0.61–3.83)		1.39 (0.56–3.49)	
Q3	1.60 (0.64–3.99)	0.481	1.47 (0.59–3.70)	0.532	1.54 (0.60–3.96)	0.157
Q4	2.05 (0.81–5.17)		1.95 (0.75–4.99)		2.03 (0.79–5.26)	
Q5 (Lowest Obesity)	1.00		1.00		1.00	
Fast food Availability	1.08 (0.98–1.20)	0.129	1.07 (0.96–1.19)	0.215	1.03 (0.92–1.16)	0.544
Fast food availability						
Not available (0)	1.01 (0.75–1.36)	0.927	1.08 (0.80 -1.44)	0.617	1.29 (0.91–1.75)	0.107
Available (> 0)	1.00		1.00		1.00	

Model 1 : Unadjusted ; Model 2: Adjusted for individual level variables ; Model 3 : Adjusted for individual level variables and neighbourhood IRSD; Odds ratios for continuous variables expressed as odds per standard deviation

Table 6. 3 : Results of multivariable regression analysis indicating the association between neighbourhood characteristics and SMI-T2D comorbidity in Illawarra – Shoalhaven (2010 – 2017)*

Variables	Model 1		Model 2		Model 3		Model 4	
	Odds ratio	P value	Odds ratio	P value	Odds ratio	P value	Odds ratio	P value
Individual variables								
Sex								
Female			1.00		1.00		1.00	
Male			0.95 (0.78 -1.17)	0.658	0.96 (0.78- 1.17)	0.687	0.96 (0.78–1.18)	0.685
Age								
18 - 44			1.00		1.00		1.00	
45–65			3.79 (2.91–4.93)		3.78 (2.90–4.92)		3.77 (2.88 - 4.92)	
65+			7.68 (5.77–10.23)	<0.001	7.82 (5.87–10.42)	<0.001	7.87 (5.89 -10.51)	<0.001
Country of birth								
Australia			1.00		1.00		1.00	
Oceania excluding Australia			1.57 (0.81–3.03)		1.53 (0.79–2.97)		1.57 (0.81 -3.04)	
UK & Ireland			0.84 (0.57–1.26)		0.88 (0.59–1.31)		0.85 (0.57 - 1.26)	
Western Europe			0.99 (0.63–1.54)		0.97 (0.62–1.52)		0.99 (0.63 -1.55)	
Eastern and central Europe			1.30 (0.82–2.05)		1.30 (0.82–2.06)		1.38 (0.87–2.19)	
South East Asia			1.30 (0.53–3.19)		1.30 (0.52–3.19)		1.25 (0.51–3.07)	
Central and South Asia			2.03 (0.53–7.82)		2.13 (0.56–8.10)		2.09 (0.55–7.98)	
Middle East and North Africa			1.84 (0.83–4.09)		1.87 (0.84–4.16)		1.94 (0.87–4.32)	
Americas			0.42 (0.06–3.25)	0.137	0.41 (0.05–3.15)	0.149	0.39 (0.05–3.04)	0.145
Neighbourhood Variables								
IRSD quintiles								
Q5 (Least disadvantaged)					1.00		1.00	
Q4					1.87 (0.77–4.53)		1.57 (0.59 -4.19)	

Q3					2.67 (1.14–6.15)		1.73 (0.65–4.67)	
Q2					2.92 (1.28–6.67)		1.97 (0.72–5.35)	
Q1(Most disadvantaged)					3.20 (1.42–7.20)	0.008	1.96 (0.69–5.51)	0.690
Area level crime								
Q5 (Lowest crime)								
Q4							1.00	
Q3							0.97 (0.34 -2.73)	
Q2							1.56 (0.57–4.27)	
Q1(Highest crime)							2.20 (0.81–5.99)	
							2.78 (1.02–7.57)	0.001
Variance of random effects								
T^2	0.098		0.073		0.056		0.012	
PCV	Ref		25.5%		42.9%		87.76%	
ICC	**0.029**		**0.0217**		**0.017**		**0.004**	

***Only significant neighbourhood variables reported**

Model 1: Null model with suburb level random effect

Model2: Model 1 + individual level factors

Model 3: Model 2 + neighbourhood level IRSD quintiles

Model 4 : Model 3 + neighbourhood variables

Discussion

We examined associations between characteristics of neighbourhood environments and the likelihood of T2D comorbidity in individuals with SMI. The results indicate that approximately 3 % of the total variance in SMI-T2D comorbidity was attributed to neighbourhood characteristics. The neighbourhood variables included in this study accounted for approximately 45 % of this neighbourhood variation and neighbourhood socioeconomic disadvantage accounted for an additional 17 % . A statistically significant positive association was observed between area level rates of crime and SMI-T2D comorbidity independent of individual-level characteristics and neighbourhood-level socioeconomic disadvantage. No significant associations were observed between the other four neighbourhood variables included: access to health care services; neighbourhood-level obesity; availability of green spaces; and availability of fast food restaurants and SMI-T2D comorbidity, suggesting that it is unlikely that these neighbourhood features have a large influence on SMI-T2D comorbidity.

Even though modest amounts of neighbourhood variance in SMI-T2D comorbidity was reported in this study, noting that the whole population is impacted by any small changes to reduce the neighbourhood disparities is important. As Geoffrey Rose has pointed out, population based approaches have the potential to shift the risk distribution of the entire population in a favourable direction and are considered more effective in reducing the disease burden than a ‘high-risk’ approach in which measures are targeted only to individuals with substantially higher risk [52].

This is one of the few studies to investigate the relationship between neighbourhood features and SMI-T2D comorbidity. To the best of our knowledge, this is also the first report of a direct association between objectively measured area level crime and T2D risk in individuals with SMI. Our results parallel those of a recent study from the United States

which reported an increased odds of depression and T2D comorbidity in neighbourhoods with higher perceived neighbourhood problems such as violence [53]. Other research has also connected perceived neighbourhood crime rate to independent T2D incidence [31, 54] as well as to the risk factors of T2D such as psychological distress, lower physical activity and obesity [17, 18, 55, 56]. Furthermore, persistent exposure to fear and stress are proposed to alter immune system response and activate the hypothalamic pituitary adrenal axis accelerating the development of T2D [1, 57].

In contrast to previous studies on independent T2D risk, we identified no significant association between SMI-T2D comorbidity and neighbourhood resources such as health care access, fast food availability and green spaces. However, one previous study by Kirkpatrick et al had reported increased T2D risk in psychosis patients independent of access to care [58]. One potential explanation for these null findings could be that individuals with SMI may have trouble changing an unhealthy lifestyle despite the availability of resources due to their psychosocial disability and cognitive impairment [59, 60]. For example, lower physical activity could be due to negative symptoms and social isolation, and neighbourhood level green space may not be a relevant resource for physical activity in individuals with SMI. Similarly, negative, and psychotic symptoms can be barriers to accessing health care services despite availability [4, 58]. The null results may also be attributable to differences in study design; neighbourhood measures assessed; the way in which constructs were evaluated (e.g. density versus distance, quantity versus quality) ; and the population examined. With regards to health care access, it should be noted that Australia has a national health care scheme (Medicare), envisioned to deliver the most equitable and efficient health care access at reduced or no cost [61]. This along with several Australian Government initiatives to improve health care access for people with mental illness may have resulted in decreased inequities in

health care access for this population. It is unlikely for an effect to be detected without variations in neighbourhood exposures. The lack of association of SMI-T2D comorbidity with health care access may also be due to the inefficiency of current primary care interventions designed for general population in reaching disadvantaged groups such as individuals with SMI, as suggested by a systematic review by Glazier et al. (2006) [62]. Hence individuals with SMI may require additional support to utilise the available resources to achieve the same effect realized by individuals without SMI. Further research is needed to draw definitive conclusions.

Strengths and limitations

Strengths of our study include a large sample of clinically coded individuals with SMI; assessment of multiple environment features; use of objectively measured neighbourhood data collected from different sources; and multilevel analysis. Limitations include the cross-sectional design which prevents us from drawing causal inferences. Individual-level data used in this study were sourced only from inpatient mental health records and did not consider outpatient and private practice records. The Australian National Surveys of Psychosis indicates that 45.6–62.9% of people with SMI reported ≥1 hospital admission for any reason in the previous 12 months [63]. As such, our eight-year data collection period should have provided a reasonable coverage of the study population. It is also possible that our results are influenced by temporal misalignment as neighbourhood level data were collected for different time periods due to the non-availability of historical data on these neighbourhood variables. Individual socioeconomic status, which is often used in neighbourhood studies, was also not available for inclusion in this analysis. Likewise, information regarding the level of diabetes and SMI control was not available for inclusion in this study. In addition, multilevel modelling approach employed in this study may be limited in its ability to provide optimal information on the spatial distribution of

outcomes, as it fragments space into arbitrary administrative areas and ignores the spatial association between them [64]. However, Moran's I statistics of area level residuals did not reveal spatial autocorrelation unaccounted by multilevel models used in this study, [65] indicating further spatial exploration is unwarranted**.** Another limitation associated with this study is the use of a single pre-defined administrative spatial unit for analysis. Consequently, these results may be affected by the modifiable areal unit problem (MAUP), which refers to the dependency of results on the definition of spatial units [66]. Nonetheless, the consistency of associations between different neighbourhood variables aggregated at administrative units and cardiometabolic risk factors observed in multiple studies provides some support for these analysis [67, 68]. We also acknowledge the limitation of using neighbourhood obesity as a proxy for neighbourhood cues for obesogenic environment. However, sensitivity analysis excluding neighbourhood obesity did not alter the results substantially indicating that the results were not sensitive to this variable.

Conclusions

Type 2 diabetes comorbidity in SMI is a major public health issue. While many studies investigating this association looked at the individual level factors, we examined the added influence of neighbourhood contextual environments on SMI-T2D comorbidity. We observed that individuals with SMI residing in areas with higher crime rates were more likely to report T2D comorbidity compared to individuals with SMI residing in lower crime rate areas, even after controlling for individual-level variables and neighbourhood-level disadvantage. The study provides a case for primary and community health stakeholders to be mindful of the neighbourhood discrepancies in SMI-T2D comorbidity. The findings support targeted neighbourhood level initiatives aimed at individuals with SMI living in high crime neighbourhoods in order to reduce the public

health burden imposed by SMI-T2D comorbidity. Overall, the study suggests that the mechanisms of neighbourhood influence on SMI-T2D are highly complex. Further research is needed incorporating longitudinal study designs, data from different geographic locations, more rigorous measurements, variables not included in this study and mediation analysis to further understand the mechanisms linking neighbourhoods and T2D comorbidity in SMI, with the aim of informing policies and practices that may reduce the burden.

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CHAPTER 7

Discussion

Type 2 diabetes (T2D) comorbidity in serious mental illness (SMI) imposes enormous personal and public health burden. This thesis examined the neighbourhood correlates of SMI-T2D comorbidity. This chapter provides a succinct overview of these study findings and discusses their strengths and limitations. The theoretical and policy implications of this work and the recommendations for future research are also detailed.

Overview of studies and key findings

The specific aims of this thesis were to:

1. Describe the geography of SMI-T2D comorbidity in the Illawarra-Shoalhaven region of NSW, Australia
2. Explore the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity
3. Evaluate the association between the neighbourhood contextual features of area level crime, access to health care services, availability of green spaces, neighbourhood level obesity, availability of fast-food outlets and SMI-T2D comorbidity

The systematic literature review reported in chapter 2 of this thesis, synthesised the body of literature examining the association between neighbourhoods and SMI-T2D comorbidity. The only research identified in this review examined the association between neighbourhood-level socioeconomic disadvantage and SMI-T2D comorbidity

and reported a positive but non-significant association between the two [1]. The aforesaid study focused solely on major depression and did not consider other forms of SMI such as schizophrenia or bipolar disorder. The above study however provided an indicative evidence of higher attributable risk of T2D in disadvantaged neighbourhoods. The review identified a lack of evidence in the research literature examining the association between neighbourhoods and SMI-T2D comorbidity and pointed to an urgent need for attention to the knowledge gap in this important area of public health.

Study 1 presented in chapter 4, addressed thesis aim 1 and examined the geography of SMI-T2D comorbidity in the Illawarra-Shoalhaven. This study also compared the geographic distribution of SMI-T2D comorbidity with the single diagnosis of SMI and diabetes in the Illawarra-Shoalhaven. Geographic variation in SMI-T2D comorbidity was examined by Moran's I at the global level [2] and the statistically significant local clusters were identified by LISA (Local Indicators of Spatial Association) and spatial scan statistic [3, 4]. The geographic convergence of SMI, diabetes and their comorbidity were assessed by generating choropleth hotspot maps and spatial scan statistics. Bivariate LISA and multivariate spatial scan were used to identify coincident areas with higher rates of both SMI and T2D [3, 4]. Suburbs were used as a proxy for neighbourhoods in this research as it was the smallest unit at which health service data were available [5].

The findings from the first study demonstrated significant geographic variation in the distribution of SMI-T2D comorbidity in the Illawarra-Shoalhaven. Consistently higher burden of SMI-T2D comorbidity was observed in six urban suburbs surrounding the major metropolitan city centre. A geographic convergence of high-risk areas was observed between SMI, T2D and their comorbidity again in four of the same urban suburbs outside the major metropolitan city centre. Both LISA and bivariate LISA clusters became non-significant after correcting for multiple comparisons using the

Benjamini Hochberg procedure. Although Benjamini Hochberg Correction is a less conservative method compared to other false rate discovery correction methods, there can still be substantial loss of power when dealing with larger datasets [6]. This loss of power could have contributed to the non-significant results in both these analyses. Nevertheless, the correspondence in results observed between uncorrected LISA hotspot clusters and spatial scan clusters indicate that these results are important [6].

This appears to be the first study to explore the geographic variations in the distribution of SMI-T2D comorbidity. However, previous research has established significant geographic inequalities and urban clustering in the distribution of both SMI and type 2 diabetes as independent conditions [7-12]. A spatial exploration by Barker et al. (2011) highlighted a high prevalence cluster of diagnosed diabetes in the southern United States referred to as the 'diabetes belt' [13]. Similar analysis has also revealed geographic variations and urban clustering in the distribution of mental illness [10, 14, 15]. The finding of higher burden of SMI-T2D comorbidity in urban areas surrounding the major city centre reported in this thesis is consistent with a population-based report from Taiwan showing higher T2D prevalence in individuals with major depressive disorder living in suburban areas [16]. Overall, the findings from study 1 suggested that the population in some urban suburbs in the Illawarra-Shoalhaven are disproportionately burdened by SMI, T2D and their comorbidity. This study also provided an impetus for taking neighbourhood factors into account in order to elucidate the correlates of SMI-T2D comorbidity.

These findings also supported further exploratory investigation using spatial clustering of SMI-T2D comorbidity as a framework. One commonly hypothesised and plausible exposure is the neighbourhood socioeconomic disadvantage [17]. Individuals with SMI are more likely to reside in socioeconomically disadvantaged neighbourhoods [11, 12]

and the environment in these neighbourhoods may expose individuals with mental illness to greater psychosocial stress, or act as a risk for adverse health behaviours such as unhealthy eating, lack of physical activity and obesity, which are associated with increased T2D risk [12, 18, 19]. Hence, an association between neighbourhood disadvantage and comorbid SMI-T2D is highly plausible, given what is known about the underlying complex mechanisms that drive these disorders.

The second study of this thesis reported in Chapter 5, addressed thesis aim 2 and investigated the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity. It was hypothesised that greater neighbourhood disadvantage would be associated with increased T2D comorbidity in individuals with SMI. A further objective of this study was to determine the amount of between neighbourhood variance in SMI-T2D comorbidity that was accounted for by neighbourhood socioeconomic disadvantage. Neighbourhood disadvantage was operationalised in this study using the Index of Relative Socioeconomic Disadvantage (IRSD) from the Socioeconomic Indexes for Area (SEIFA) Census product [20]. An IRSD score reflects a region's socioeconomic disadvantage measured on the basis of seventeen variables including education, income, occupation, unemployment, housing type, overcrowding and English proficiency [20]. Multilevel logistic regression models accounting for neighbourhood-level clustering were used to assess these associations. A multilevel modelling approach in this case allowed the use of data at two different levels: individuals at level 1 nested within suburbs at level 2. Models were adjusted for age, sex and country of birth.

A significant positive association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity that remained after controlling for individual level variables was identified in study 2. Residents in the most disadvantaged neighbourhoods had 3.2 times increased odds of having SMI-T2D comorbidity compared with the residents in the

least disadvantaged neighbourhoods (95% CI 1.42-7.20). Among the individual level factors, age was found to be significantly associated with SMI-T2D comorbidity. No independent association was observed between gender or country of birth with SMI-T2D comorbidity. Study 2 also revealed small but significant neighbourhood level variation in the distribution of SMI-T2D comorbidity (Median Odds Ratio = 1.35, Intra Class Correlation = 0.03) [21]. Neighbourhood socioeconomic disadvantage explained 17.3% of this variation. No evidence of interaction was observed between neighbourhood disadvantage and the individual-level variables included in the study. It was observed that the 95 % confidence intervals for the association between neighbourhood disadvantaged quintiles and SMI-T2D comorbidity overlapped indicating a weaker association than observed and should be regarded cautiously given the small sample sizes in the quintiles. Nonetheless, it should be noted that overlapping confidence intervals does not always imply that there is no statistical difference between the two groups. Sensitivity analysis using neighbourhood disadvantage as quartiles did not change the results significantly.

This was one of first studies to explore the association between area level disadvantage and SMI-T2D comorbidity. The only other research addressing this association investigated major depression alone and reported a positive but non-significant association between neighbourhood level disadvantage and depression-T2D comorbidity [1]. However, the results from study 2 are consistent with prior epidemiological reports, which show significant neighbourhood level socioeconomic inequities in the distribution of SMI [22-24] and T2D [9, 25-27] as independent conditions. Previous systematic literature reports have also underlined the influence of neighbourhood socioeconomic status on SMI and T2D when considered separately [28, 29]. The findings of a positive significant association of SMI-T2D comorbidity with age and a non-significant association with gender are also consistent with previous findings [30-32].

The modest area level variance in SMI-T2D comorbidity reported in this study does not preclude important area level effects. Misspecification of neighbourhoods, smaller group sizes and even non-inclusion of a relevant level 1 variable can all cause under estimation of neighbourhood variance [33, 34]. Several examples are available in public health where low ICC coexisted with important neighbourhood level fixed effects, i.e. where risk factors explain small amounts of neighbourhood variance but are important predictors of health outcomes [33]. For example, a study by Tu et al. (2014), which demonstrated the contextual effect of neighbourhood socioeconomic status on the risk of pre-term births [35]. Moreover, even small neighbourhood level effects can have large impacts when aggregated to population levels as noted by Geoffrey Rose [36].

The findings from study 2 highlighted the need to consider health strategies at both individual and neighbourhood level in order to reduce the public health burden imposed by comorbidity. The results also suggested that the efforts to reduce diabetic comorbidity in serious mental illness might benefit by focussing on individuals with SMI living in disadvantaged neighbourhoods. A plausible explanation for the higher SMI-T2D comorbidity risk in disadvantaged areas may be the reduced availability of neighbourhood resources as posited by the Social Determinants of Health (SDH) theory [37]. This may act as a stimulus for chronic stress or adverse health behaviours such as unhealthy eating, insufficient physical activity and obesity, which are associated with increased T2D risk [12, 18, 19]. For example, disadvantaged neighbourhoods may lack access to fresh produce and be dominated by fast food and convenience stores, making the latter the easily available food option [38]. Similarly, disadvantaged neighbourhoods might lack an environment conducive to physical activity [31]. As many of these neighbourhood factors were not included in the socioeconomic indexes used in study 2, further exploration and identification of specific neighbourhood level characteristics

associated with T2D risk in SMI was considered appropriate in order to advance our understanding of the T2D comorbidity in SMI. Information on the association between specific neighbourhood level features and SMI-T2D comorbidity would also be useful and informative for developing policy solutions and interventions.

Study 3 presented in Chapter 6, addressed thesis aim 3 and investigated the association between five neighbourhood contextual variables and SMI-T2D comorbidity. The relevant neighbourhood indicators of T2D risk previously identified in the literature such as area level crime, accessibility of healthcare services, availability of green spaces, neighbourhood obesity and neighbourhood fast food availability were examined. Obesity was used as a contextual variable in this study as the information on individual-level obesity was not available. Moreover, neighbourhood environments are reported to provide cues that support social norms defining individuals' healthy behaviours, which can be compromised neighbourhoods with higher rates of obesity [39]. A series of multilevel logistic regression models accounting for neighbourhood level clustering were used to examine the associations between five neighbourhood variables mentioned and SMI-T2D comorbidity in this study, sequentially adjusting for individual-level variables and neighbourhood-level socioeconomic disadvantage.

The results from study 3 demonstrated a significant positive association between area level crime and SMI-T2D comorbidity independent of individual level characteristics and neighbourhood level socioeconomic disadvantage. Individuals with SMI residing in highest crime areas were more likely to have T2D comorbidity compared to SMI individuals residing in lowest crime areas (OR 2.78, 95% CI 1.02 – 7.57). No evidence of association was observed between the remaining neighbourhood variables examined and SMI-T2D comorbidity. The ICC for the null model was 0.029, indicating that 2.9% of the variance in SMI-T2D comorbidity was attributable to between neighbourhood

differences. Addition of all the neighbourhood features accounted for 87.76% of between area variance and the ICC was reduced to 0.004 in the final model, indicating that the majority of residual variance in SMI-T2D risk was attributed to within neighbourhood rather than between neighbourhood differences. Sensitivity analysis excluding neighbourhood level obesity did not change the results substantially indicating that the results were non-sensitive to this variable. No evidence of interaction was observed between neighbourhood and individual variables. Sensitivity analysis was also undertaken using area level crime, health care access and neighbourhood obesity as quartiles and using three levels (tertiles) of fast food availability (0, 1-2, 3+). Although quartile confidence intervals were smaller indicating greater precision, the overall effect estimates, and significance remained the same and did not materially affect the reported conclusions drawn using quintiles. This sensitivity analysis is included as Appendix K.

It was observed that the addition of area level crime diminished the statistically significant association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity. One possible explanation may be the mediation role played by area level crime in the relationship between neighbourhood disadvantage and SMI-T2D comorbidity. A mediator is on the casual pathway between the dependent and independent variable and may partially explain the strong effect or lack of effect between the two [40]. As the explicit objective of mediation analysis is to demonstrate casual relationships, longitudinal study designs are required to accurately reflect mediation effects and was hence beyond the scope of this study [41]. It could also be due to the correlation between these two independent variables [42]. There is considerable research literature available, reporting on the consistent positive correlation between area level disadvantage and crime [43]. Moreover, many of the variables that are used in computing the Index of Relative Socioeconomic Disadvantage (IRSD), such as low income, unemployment etc

[20] are historically associated with higher crime and violence [44]. The observed variance inflation factors for IRSD (2.72) and crime (1.89) did not indicate multicollinearity in this study, which provides some evidence against the dependency between these variables. However, it remains plausible that crime and disadvantage are measuring the same or similar construct and, as such, may compete to explain the same variance. Another reason may be the loss of degrees of freedom associated with estimating many parameters from a given dataset [45]. This may affect the power and precision of the model estimates leading to lower t statistics and higher p values [45].

This study is also one of few studies to examine the association between neighbourhood features and SMI-T2D comorbidity. This is also a first report of a direct association between objectively measured neighbourhood level crime and T2D risk in individuals with SMI. These results parallel those of a recent study from the United States which reported an increased odds of depression and T2D comorbidity in neighbourhoods with higher perceived neighbourhood problems such as violence [46]. Other research has also connected perceived neighbourhood crime rate to T2D incidence [47, 48] as well as to the risk factors of T2D such as psychological distress, lower physical activity and obesity [18, 49-51]. Furthermore, studies have found that chronic exposure to persistent fear and stress can activate the hypothalamic pituitary adrenal and sympathetic adrenal axes through a process described as allostasis, accelerating the development of T2D [31, 52]. Residents' beliefs, or perceptions, about the safety of their neighbourhood were also shown previously to influence their behaviour thus influencing T2D risk [47]. A systematic review synthesising qualitative evidence from United Kingdom had also suggested an important role played by fear of crime in mediating environmental impacts on health and wellbeing mainly by acting as a barrier for outdoor activities [53]. The study finding also contrasts with a few studies which reported no significant association

between neighbourhood crime rates and independent T2D incidence [54-56]. However, all of these studies relied on perceived neighbourhood crime measurements and a direct comparison with our results are not possible due to difference in study design and population.

The findings from study 3, did not identify any significant association between neighbourhood resources such as health care access, fast food availability and green spaces with SMI-T2D comorbidity. These results are in contrast to previous studies on the risk of T2D as an independent condition [57-60]. However, a previous study by Kirkpatrick et al. (2010) reports an increased T2D risk in a sample of newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis, independent of the access to care, which is consistent with study 3 findings [61]. The finding of no association between neighbourhood resources and SMI-T2D comorbidity observed in this study could be due to the difficulties faced by individuals with SMI in making behavioural changes despite the availability of resources, due to their psychosocial disability and cognitive impairment [62, 63]. For example, lower physical activity could be due to negative symptoms and social isolation, and neighbourhood level green space may not be a significant resource for physical activity in individuals with SMI. Similarly, negative and psychotic symptoms can be barriers to accessing health care services despite their availability [61, 64]. The mixed findings may also be due to the differences in study design; neighbourhood measures assessed; the way in which constructs were evaluated (e.g. density versus distance); and the population examined in this thesis. For instance, in the study by Astell Burt et al. (2014) [65], which reported lower odds of prevalent diabetes associated with total green space, percentage green cover within a 1.6 km road network buffer (based on the published guideline on distance that can be covered by foot [66]) was used as the green space measurement in contrast to the percentage green cover in the entire

neighbourhood unit used in the current study. Nonetheless, study 3 findings highlighted the influence neighbourhoods may have upon SMI-T2D comorbidity and suggested the potential for geographically targeted initiatives in high crime neighbourhoods in order to reduce the public health burden imposed by the comorbidity.

Theoretical implications of the thesis

The findings from this thesis are consistent with the social ecological model by Rudolph Moss, which recognises multiple levels of influences on health behaviours [67]. Ecological models in general focus on peoples' transactions with their physical and social environments. It is these levels of environmental influence that distinguishes ecological from behavioural models of health [68]. The central concept is that a combination of individual, environmental and policy level factors are responsible for health outcomes in individuals [68]. In other words, health behaviours are considered to be maximised when environments and policies support individual level influences. Hence, an individual well informed of the benefits of physical activity living in a neighbourhood with less physical activity resources may not be able to maximise their potential for better health. According to socioecological theories, the environmental influences are also posited to interact across levels affecting the health behaviour [69]. Rudolph Moss's social ecological model recognises four levels of environmental influences on health behaviour: (1) physical setting – refers to the features of natural and built environments, (2) organisational setting – refers to the size and function of workplaces and schools, (3) human aggregate – refers to the sociocultural characteristics of the individuals and (4) social climate – refers to the social setting [67].

Most previous studies on SMI-T2D comorbidity focused only on individual level variables and have not recognised the relative importance of physical and social environmental influences on comorbidity [64]. The current study addressed this gap by

examining different levels of environmental correlates of SMI-T2D comorbidity and their interactions. This thesis investigated variables from all four levels of neighbourhood influence on SMI-T2D comorbidity as proposed by Rudolph Moss's model. The variables studied were: age, sex and country of birth from the human aggregate level; area level crime, neighbourhood obesity and neighbourhood disadvantage from the social climate level; green space and fast food restaurants from the physical setting; and access to health care from the organisational setting. Findings from this study provided some evidence for the multilevel principle of the Moss's social ecological framework. However, no evidence of interaction across levels were observed. A similar observation of multilevel effect without interactions were also reported by Giles-Corti and Donoven (2002) while studying the influence of psychological, social, and physical environment variables on physical activity [70].

The key strength of social ecological approach is that it broadens options for planning interventions [68]. Policy and environmental changes have the potential to influence the entire population in contrast to individual level interventions that reach only the individuals who are willing to participate. However, a key weakness is the lack of specificity about the environmental influence, which makes it difficult for public health researchers to identify the critical factors for interventions [71]. For example, in this study neighbourhood socioeconomic disadvantage was identified as a correlate of SMI-T2D comorbidity. However, the lack of specificity about what comprises this disadvantage makes it challenging to design useful interventions based on this result. Another drawback of this approach is the difficulty and time needed to make environmental changes and policies [68]. Most environmental policy changes are not controlled by public health professionals and need to go through a political process, and these can be time consuming. In this study area level crime was identified as an environmental

influence on SMI-T2D comorbidity. However, crime reduction strategies need to be enacted politically. In addition, health professionals have to become skilled in advocacy and political change in order for these processes to happen [68]. Overall, this study complemented the literature available on the individual correlates of SMI-T2D comorbidity. The next research priority should be to advance our understanding of the multilevel correlates of SMI-T2D comorbidity to inform effective intervention strategies.

Strengths and limitations of the thesis

This thesis is one of the first studies to consider associations between neighbourhoods and T2D comorbidity in SMI. In doing so, it has made important contributions to addressing the lack of evidence highlighted in the literature review about this area of public health. Another strength of this study is the use of spatial analysis in chapter 4 and multilevel modelling in chapters 5 and 6, allowing effective investigation and illustration of neighbourhood effects on SMI-T2D comorbidity. Spatial analysis is a well validated approach for describing geographic variation in disease prevalence, which allowed for the identification of critical regions of SMI-T2D comorbidity to focus on, with important implications for public health policy as described above [72].

The multilevel modelling approach used in this study made it possible to use data at different levels to describe the relationship between neighbourhoods and SMI-T2D comorbidity [73]. This thesis used individual level data nested within suburbs to account for shared exposures to the same levels of neighbourhood factors. Had the data been available only at a neighbourhood level, the investigation would have been an ecological study. Ecological studies lack individual information and are unable to differentiate between contextual and compositional effects. Interpreting neighbourhood level predictors as individual predictors may result in mistaken inferences commonly referred to as ecological fallacy [74, 75]. Similarly, if data were available at only individual level,

predicting group outcomes based on individual only data would have resulted in erroneous inference commonly referred to as atomistic fallacy [75]. Apart from atomistic fallacy, failure to account for clustering of individuals within neighbourhoods may lead to underestimation of standard errors and can also fundamentally change the size and magnitude of parameter estimates [76, 77]. By using multilevel models which included variables measured at both individual and the neighbourhood level, it was possible to reduce the risk of both ecological and atomistic fallacies. It also ensured that the standard errors were corrected for the nonindependence of individuals within neighbourhoods.

The large sample of clinically coded individuals with SMI used in this thesis should also be considered a strength. The inpatient data used in this study were clinically coded and included all the established diagnostic codes to capture SMI and was considered highly accurate [78, 79]. These diagnostic codes are used by health care services for management purposes and there are financial imperatives associated for them to be complete and accurate. Data from approximately 4000 individuals with SMI were investigated in this study, which is a relatively larger sample size compared to similar research in the area .

Another strength of this thesis is the large number of objectively measured neighbourhood variables examined. The use of objective data is reported to improve the strength of the research findings by eliminating the probability of reporting bias [80]. Many previous neighbourhood studies on T2D risk have used self-reported neighbourhood measures such as perceived neighbourhood crime. For example, McCurley et al.(2019) studied the associations between perceived neighbourhood violence and depression-T2D comorbidity [46]. Perceptions of experience and environmental surroundings are reported to be influenced by the psychological well-being and mood of the respondents in the same study, with individuals having greater depression reporting greater neighbourhood violence [46].

As with any research, there are a number of potential limitations to this thesis and the findings should be interpreted with considerations to these limitations. First, the cross-sectional study design of this research limits the cause and effect conclusions that can be drawn from this study. Neither can the study ascertain whether individuals with SMI-T2D comorbidity lived in a certain neighbourhood by choice or because they were financially restricted to live in these neighbourhoods (reverse causation).

Second, the serious mental illness and comorbidity data used in this thesis were sourced only from the inpatient records of Illawarra Shoalhaven Local Health District (ISLHD) and did not consider outpatient and private practice records. Nevertheless, Australian National Surveys of Psychosis found that 45.6 - 62.9% of people with SMI reported ≥1 hospital admission for any reason in the previous 12 months [81], which should have provided a reasonable coverage given the 8-year data collection period.

Another limitation with this study, is the use of readily available census tracts units (suburbs) as the proxy for neighbourhoods, as it was the spatial unit at which health service data were available. The choice of right neighbourhood scale is a critical factor, while examining neighbourhood effects. Two problems commonly associated with the inappropriate choice of spatial units are the Modifiable Areal Unit Problem (MAUP) and the boundary effects [82, 83]. MAUP is a problem of artificial spatial patterning arising from the imposition of artificial geographic units of varying sizes and aggregation levels on continuous geographical phenomenon [82]. The implication is that the results of spatial data analysis might change depending on the number and scale of spatial units used to define an area. Another common problem is the edge or boundary effects, which are the errors in analysis caused due to the placement of a study boundary [83]. For example, when neighbourhoods are defined as suburbs, the residents who live next to the boundary of a suburb are treated identically to those residing at the centre. However, it is

likely that the residents who live next to a boundary spend an appreciable amount of time in the adjacent suburb and are therefore exposed to neighbourhood environments there. Consequently, the assignment of a neighbourhood exposure to all individuals in a suburb may result in a measurement error. Creation of buffers around individual addresses has been proposed as a solution to this problem [84]. However, this was not possible in this research due to the non-availability of patient addresses.

In addition, multilevel modelling approach employed in this thesis may be limited in its ability to provide optimal information on the spatial distribution of outcomes, both when measuring variations and investigating associations as it fragments space into arbitrary administrative areas and ignores the spatial association between them [85]. However, Moran's I statistics were computed for the area level residuals in study 2 and study 3 in order to check for the spatial autocorrelation unaccounted by multilevel models used in this study [85]. In this case, Moran's I showed whether adjacent neighbourhoods (sharing a common boundary or edge) had more similar area level residuals than one would expect at random. The Moran's I results nonetheless revealed no spatial autocorrelation between residuals in both study 2 and study 3 models, indicating that further spatial exploration is unwarranted (Appendix I).

A further limitation with the multilevel logistic regression used in this thesis is that the interpretation of odds ratios is conditional upon the random effect being held constant and this conditional interpretation can be problematic when considering a model that incorporates cluster or neighbourhood-level characteristics [86] such as Study 2, Model 3. In Model 3, the odds ratio of SMI-T2D comorbidity for the most disadvantaged neighbourhood quintile compared with the least disadvantaged quintile was 3.20. The conditional interpretation of this result is that, after fixing the individual characteristics and the random effect, an increase in disadvantage quintile from most to least is associated

with 3.2 times increase in the odds of SMI-T2D comorbidity. Thus, for any given neighbourhood, an increase in disadvantage from most to least is associated with 3.2 times increase in odds of SMI-T2D comorbidity. This interpretation is considered problematic as neighbourhood disadvantage is fixed within a neighbourhood. In order to address this limitation, population averaged odds ratios were approximated from the conditional multilevel regression coefficients as suggested by Austin and Merlo (2017) [87]. The population average odds ratio is the average odds ratio comparing two individuals from two different neighbourhoods who are identical in other respects apart from the covariate of interest [88]. Since these associations are not cluster specific, the interpretation of an association between a neighbourhood variable and SMI-T2D comorbidity is easier. The approximated population-average odds ratios for the neighbourhood socioeconomic disadvantage in Model 3 were essentially equal (3.16 for Q1 Vs Q5) to the cluster specific odds ratios indicating that these results are important (Appendix J)

There is also the potential for temporal misalignment as 2011 data were used as the reference population in study 1 and 2. Data from 2011 Census were used in this thesis as Southern IML Research study (SIMLR) database is presently geocoded to 2011 boundaries. Data custodians are working with Southern IML pathology to include 2016 data, but this will not be available until later in 2020. Similarly, potential for temporal misalignment is also acknowledged for study 2 and 3 as many of the neighbourhood data variables used were from different points in time. Sensitivity analysis was carried out whenever data were available for two different time periods. For instance, neighbourhood socioeconomic disadvantage was operationalised for suburbs using the Index of Relative socioeconomic disadvantage (IRSD) from the 2011 Socioeconomic Indexes for Area Census product. However, a weighted Kappa analysis was carried out between 2011 and

2016 disadvantage quintiles. The results indicated that the deprivation scores have remained relatively similar during these periods (k = 0.80)

It should be noted that several of the individual variables that may be relevant in SMI-T2D comorbidity such as individual socioeconomic status, ethnicity, age at diagnosis, number of hospital admissions and antipsychotic use were not available and could not be included in this analysis. This may have resulted in the overestimation of neighbourhood level effects [89]. Country of birth included in this study has been used as a proxy for ethnicity previously [90, 91]. However, it is a less accurate measure of ethnicity as it does not consider the ethnic diversity of a single country of origin or the ethnic background of second-generation immigrants [90]. Similarly, several neighbourhood level variables that may be relevant for individuals with SMI such as neighbourhood social support and air / noise pollution were also unavailable for analysis and may have contributed to biased estimates. A study conducted in United States among the south Asian population had found that individuals living in neighbourhoods with higher perceived social cohesion had 43 % reduced odds of having hypertension than those living in neighbourhoods with lower social cohesion [92]. Psychosis incidence was also shown to higher in socially isolated neighbourhoods [93]. Similarly, air and noise pollution were reported to be associated with both psychotic experience and T2D [94-96]. Further research is required to ascertain the contribution of a broad range of neighbourhood variables with SMI-T2D comorbidity.

It is acknowledged that the exploration of the effect of multiple variables on SMI-T2D comorbidity adopted in this study may increase the risk of finding significant results by chance (type 1 error) due to the problem of multiple testing or multiple comparison [97]. However, it has been argued that multiple testing corrections are not warranted while adhering to a statistical hypothesis testing framework especially in the case of exploratory

studies [98, 99]. This is because the formulation of multiple testing problem is already predicated in the universal null hypothesis that only random processes determine the variability of observations in hand [99]. Under this framework, the objective of the study is to evaluate data for its compatibility with the universal null hypothesis [98]. Multiple testing corrections are considered appropriate in the case of confirmatory studies, where the knowledge is sufficiently advanced to formulate specific hypothesis [99], which was not the case with the current study. Moreover, multicollinearity can lead to type 1 error by inflating the value of estimated coefficients and their standard errors. However, multicollinearity was not evident in this study, which reduced the likelihood of falsely rejecting a true null hypothesis (type 1 error), as the coefficient estimates are generally considered stable and not influenced by other variables [100].

Residential location at last rather than first inpatient admission was used to assign neighbourhood variables in this study instead of first admission. This was done to reflect the current trends in neighbourhood resources and population needs. Moreover, residential location available in Illawarra Health Information platform is based on a person's most recent stay and the historical residential information is unavailable on the data platform. Hence these results may be subjected to inferential bias as the residential mobility of individuals with SMI was not accounted for in this analysis. The classic theories on residential mobility posits that an individual's economics and demographic factors determine their residential locations [101]. People with SMI are often claimed to be affected by residential instability and drift to lower socioeconomic and high crime neighbourhoods following disease incidence , which leaves open the possibility for reverse causation [102]. However, a large longitudinal cohort study from United States pointed out that the higher drift found in individuals with schizophrenia was largely explained by their pre-existing socioeconomic conditions than the disease diagnosis itself

[103]. Residential instability experienced by individuals with SMI is also alleged to affect their health service use and disease prognosis [104]. Nonetheless, examining the residential mobility of individuals with SMI and the possibility for reverse causation was beyond the scope of the current thesis due to the cross-sectional nature of the data and the lower sample size. However, it is acknowledged that this is an important consideration in SMI-T2D comorbidity and should be explored in future research.

This thesis was also unable to control for the residential selection of SMI individuals into neighbourhoods [105]. Residential self-selection or residential sorting occurs when individuals choose to be in a neighbourhood due to their personal preferences or through their social or economic circumstances [106]. For example, healthy individuals may self-sort themselves into neighbourhoods with health promoting resources. Alternatively, unhealthy individuals may relocate to more disadvantaged, high crime neighbourhoods due to their lower socioeconomic status. This self-selection can induce bias that can potentially overinflate neighbourhood associations [107]. It may also lead to measurement error as the neighbourhood preferences are erroneously assumed to be uniform across all individuals [107]. A study from The United States, tried to address the issue of residential self-selection in neighbourhood-depression research by measuring the neighbourhood exposures in both monozygotic (identical) and dizygotic (fraternal) twins [108]. They thereby aimed to control self-selection by identifying matched individuals with same genetic makeup and childhood environment factors. The findings suggested that neighbourhood socioeconomic disadvantage showed a significant within pair effect on depression even after controlling for self-selection [108]. Similarly, an Australian longitudinal study found that the associations between neighbourhoods and type 2 diabetes persisted after accounting for some predictors of residential self-selection [48].

A limitation specific to study 3 was the use of density measures for neighbourhood variables such as health care access, green space and fast food availability as opposed to distance measures due to the lack of availability of patient addresses and the road network data. This could have resulted in not accounting for neighbourhood resources that are closer to the individuals but outside their neighbourhood (as explained before in the boundary effects) and may have contributed to the null findings in this study. Had road network data been available, enhanced 2SFCA methods could have been adopted for calculating the healthcare accessibility index by applying multiple travel time zones [109] or by assigning weights according to decay functions within each catchment [110, 111]. These methods would have provided a more nuanced index score without the assumption of constant access within the entire neighbourhood. Another limitation with the neighbourhood measures was that the quality of neighbourhood resources was not considered in this analysis due to the lack of readily available information. For instance, this study only considered the amount of neighbourhood green space as the green space measure and did not consider the quality or the type of the neighbourhood green space.

It is also acknowledged that area level crime may be clustered in socioeconomically disadvantaged areas due to discriminatory enforcement and judicial practices [112] and may have contributed to dependency bias [113] in these estimates. There is considerable research literature available reporting on the consistent positive association between area level disadvantage and crime [43]. Moreover, many of the variables that are used in computing IRSD, such as low income and unemployment are historically associated with higher crime and violence [44]. The observed variance inflation factors for IRSD (2.72) and crime (1.89) did not indicate multicollinearity in this study, which provides some evidence against dependency bias. However, it remains plausible that crime and disadvantage are measuring the same or similar construct and, as such, may compete to

explain the same variance. Similarly, neighbourhood obesity and access to fast food outlets may be in part measuring the same neighbourhood exposure. Nonetheless, VIF analysis did not reveal any evidence of multicollinearity (VIF 1.42 for neighbourhood obesity and 1.12 for fast food data).

It was observed that the 95% confidence intervals for the association between neighbourhood disadvantaged quintiles and SMI-T2D comorbidity overlapped indicating a weaker pairwise association and should be interpreted with caution, given the small sample sizes in the quintiles. Nonetheless, it should be noted that overlapping confidence intervals do not always imply that there is no statistical difference between the groups [114]. This is due to the margin of error associated with each group estimate. Confidence interval estimates are often comprised of sample statistics subject to a margin of error [115]. The precision associated with estimates can be affected by sample size, data variance and confidence levels at which sample statistics are estimated [115]. However, future research to confirm these associations may be beneficial. Sensitivity analysis using neighbourhood variables as quartiles was undertaken and is available in the appendix (Appendix K). The results and conclusions from this analysis remained the same as those reported in Chapter 5.

Loss of power in the pair wise comparison of odds ratios, due to categorisation is also acknowledged as a potential limitation. However, it should be noted that the omnibus test of the main effect retains the same power regardless of how its levels are parameterised [116].

Recommendations for future research

The following recommendations are suggested for future research based on the study findings: (i) use of longitudinal and qualitative study designs; (ii) use of more rigorous

neighbourhood measurements to verify the results; (iii) incorporating neighbourhood and individual level variables not included in the current analysis and (iv) expansion of assessment to include mediation analysis.

First, in the future it would be useful to use longitudinal study designs to provide stronger evidence for the relationships between neighbourhood factors and T2D comorbidity in SMI and to explore the residential mobility experienced by individuals with SMI and its effect on T2D comorbidity. This may improve our understanding of comorbidity pathways and disease-neighbourhood interactions, and may strengthen the research endeavour as well as the translation of research to practice [117]. For example, individuals with SMI may change neighbourhoods over time and similarly neighbourhood characteristics can change over time influencing individuals' exposure to a neighbourhood feature [17]. Moreover, prolonged exposures to neighbourhood features can accumulate risk factors over time. Thus, longitudinal study designs measuring both individual and neighbourhood characteristics over time can provide stronger evidence as the exposure-outcome risks can be evaluated prospectively within a hypothesis testing framework [60]. Qualitative study designs may also help to further elucidate the current results. Using mixed-methods designs may provide better insight into the motivations and insights of individuals with SMI in using neighbourhood resources and may contribute to a better understanding of the disease processes [118]. Many studies of neighbourhood effects involving individuals with mental illness often rely on self-reported measurement for neighbourhood exposures and health outcomes [60, 119]. This can be problematic as individuals with severe mental illness are reported to have a general tendency towards negative perceptions regarding their environment and health [120]. A significant association between stress and self-reported symptoms of coronary heart disease has been reported previously [112]. Similarly, individuals with depression are more likely to report

negative neighbourhood problems such as lower social cohesion [41]. Hence an objective measurement of neighbourhood exposures and health outcomes are more likely to produce a less biased picture on the relationship between neighbourhoods and SMI-T2D comorbidity in these population. Impaired decision-making capacity of individuals with SMI is also often posed as a challenge while undertaking neighbourhood studies [113]. Greater consideration of individual capacities, needs and impairments while developing research and ethical approaches are there for needed to establish and maintain participation in this population [113]. It would also be beneficial to undertake a sub analysis in individuals with schizophrenia and major depression as the comorbidity burden was found to be higher in these two subgroups. This was not possible in this thesis due to the lower number of individuals in these subgroups.

Second, future research should replicate the findings of Study 3 using more rigorous neighbourhood measurements. For example, using a road network-based health care accessibility index instead of the density-based measure used in the current study [121]. This would assist in better quantification of the association neighbourhood environments have on SMI-T2D comorbidity. Another option would be to confirm the results using different neighbourhood scales and aggregations [122].

Third, in order to confirm the neighbourhood effects on SMI-T2D comorbidity, more research is needed incorporating other individual level variables not included in this study. Examples include individual socioeconomic disadvantage and antipsychotic use [64]. Similarly, future analyses should be expanded to include neighbourhood variables not included in the current analysis, for example, walkability and social support. Future research should also focus on the quality of neighbourhood resources and its association with SMI-T2D comorbidity, for example, quality of health care services and quality of green space.

Lastly, future studies should consider the possible role of mediators in the complex causal pathway as this will help to elucidate the possible mechanisms through which neighbourhoods affect SMI-T2D comorbidity. A mediator is on the casual pathway between the dependent and independent variable and may partially explain the strong effect or lack of effect between the two [40]. As the explicit objective of mediation analysis is to demonstrate the causal relationships, longitudinal study designs are required to accurately reflect mediation effects [41]. In study 3, addition of area level crime diminished the previously significant association neighbourhood socioeconomic disadvantage had on SMI-T2D comorbidity. Future studies may find that the association between neighbourhood disadvantage and SMI-T2D comorbidity is mediated by area level crime.

Implications for policy

The findings presented in this thesis have important policy implications. The finding that SMI-T2D comorbidity is geographically clustered is relevant to health service planning and commissioning. This invites stakeholders to be mindful of the regional discrepancies in SMI-T2D comorbidity while allocating health care resources and services.

The study results also suggest that efforts to reduce the burden of SMI-T2D comorbidity may benefit from focusing on individuals with SMI living in socioeconomically disadvantaged and high crime neighbourhoods as higher risk for SMI-T2D comorbidity was observed in these neighbourhoods. However, further evidence is required to determine what drives these inequalities so that preventive interventions can be designed and implemented. Health and educational programs targeting these high-risk areas may be beneficial in reducing the burden of SMI-T2D comorbidity. Focusing interventions on high risk neighbourhoods is reported to have spill over effects beyond individual-level interventions [123]. For example, Cincinnati Children's Hospital Medical Centre in

United States, recently was able to reduce the preventable health care use among children with asthma by about 20 %, by focusing on two neighbourhoods identified as high risk in 2015 [123]. This pilot 'hotspot' based approach implemented a comprehensive program, which included outreach to children to ensure they had their medications, a transitional care team while leaving hospital, partnerships with local school and community organisations and community presentations. In individuals with SMI, lifestyle interventions have been reported to be effective in reducing T2D risk factors in the short term [124]. However, there are no previous reports available regarding the implementation of these interventions at a neighbourhood level.

People with SMI, especially schizophrenia, are reported to be less able to make lifestyle change in response to an intervention due to their cognitive decline [62, 63]. Hence, individually tailored interventions are recommended for this population [64]. The capability approach articulated by Amartya Sen may be useful in this instance [125]. Sen's framework argues that individuals differ in their capabilities to convert resources (e.g., green spaces, health care resources) into valued functioning (e.g., use as physical activity resource, utilise health care services) [125]. People with SMI may require additional support to utilise the available resources to achieve the same effect realized by individuals without SMI. Hence population level interventions need to focus not only on the resource inputs and desired outcomes but also on the capabilities of individuals attempting to utilise those resources [126].

The thesis results may also be relevant for government planning services while allotting social housing services for people with SMI. In Australia, nearly 40% of the individuals with SMI utilise community housing services [81]. The findings suggest that policies should reduce the allocation of SMI individuals into community housing options in disadvantaged and high crime neighbourhoods. These policy changes however will

require multidisciplinary collaboration and widespread support from general public and political leaders [127]. Strategies to reduce the vulnerability experienced by individuals with SMI in disadvantaged neighbourhoods are also essential. One such example is modifying the effect of exposures by investing in crime reduction and poverty reduction strategies. There is however little evidence in the peer reviewed literature regarding the implementation and evaluation of such neighbourhood strategies on individuals with mental illness.

Even though modest amounts of neighbourhood variance in SMI-T2D comorbidity were explained by the neighbourhood factors in this study, noting the whole population is impacted by any small changes to reduce the neighbourhood disparities in T2D risk is important. Population based approaches have the potential to shift the risk distribution of the entire population in a favourable direction and are considered more effective in reducing the disease burden than a 'high-risk' approach in which measures are targeted only to individuals with substantially higher risk [36]. Focussing on a neighbourhood of people with a small elevation in SMI-T2D risk may contribute more to the reduction in disease burden than focusing on the smaller number of people exposed to higher risk.

Conclusion

T2D comorbidity in SMI is a major public health issue. The studies presented in this thesis have provided several key findings which contribute to the scant literature available on neighbourhoods and SMI-T2D comorbidity. The findings demonstrate a small but important association between neighbourhood environments and T2D comorbidity in SMI. These findings indicate a potentially important role for geographically targeted initiatives designed to enhance the management of SMI-T2D comorbidity especially in disadvantaged and high crime neighbourhoods. Overall, this thesis provides a case for policy makers and health service commissioning to consider the importance of

neighbourhoods while planning treatment and preventive interventions for SMI-T2D comorbidity. Future research should incorporate longitudinal study designs, data from different geographic locations, and mediation analyses to further elucidate the mechanisms linking neighbourhoods and T2D comorbidity in SMI.

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Appendix A: Literature review published article.

Journal of Primary Care & Community Health
Volume 9: 1–7

DOI: 10.1177/2150132718802025
journals.sagepub.com/home/jpc
SAGE

Serious Mental Illness, Neighborhood Disadvantage, and Type 2 Diabetes Risk: A Systematic Review of the Literature

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Abstract

Aim of the Study: This review aims to systematically synthesize the body of literature examining the association between neighborhood socioeconomic disadvantage and serious mental illness (SMI)–type 2 diabetes (T2D) co-occurrence. **Methods:** We conducted an electronic search of four databases: PubMed, Scopus, Medline, and Web of Science. Studies were considered eligible if they were published in English, peer reviewed, quantitative, and focused on the association between neighborhood disadvantage and SMI-T2D comorbidity. Study conduct and reporting complied with PRISMA guidelines, and the protocol is made available at PROSPERO (CRD42017083483). **Results:** The one eligible study identified reported a higher burden of T2D in persons with SMI but provided only a tentative support for the association between neighborhood disadvantage and SMI-T2D co-occurrence. **Conclusion:** Research into neighborhood effects on SMI-T2D comorbidity is still in its infancy and the available evidence inconclusive. This points to an urgent need for attention to the knowledge gap in this important area of public health. Further research is needed to understand the health resource implications of the association between neighborhood deprivation and SMI-T2D comorbidity and the casual pathways linking them.

Keywords

neighborhood disadvantage, socio economic disadvantage, serious mental illness, comorbidity, type 2 diabetes

Mental disorders that are severe in degree, persistent in duration and produce significant functional impairment are referred to as serious mental illness (SMI).[1] Individuals with SMI have higher risk of premature mortality and a reduced life expectancy of approximately 10 to 30 years compared with the general population.[2-4] A large proportion of this excess mortality experienced by people with SMI is the consequence of cardiovascular diseases for which type 2 diabetes (T2D) is a major risk factor.[4-6]

The prevalence of T2D in people with SMI is two to four times higher than the general population with estimates ranging from 1% to 68%.[7-11] In those with SMI, a comorbid diabetes diagnosis not only confers a higher cardiovascular risk and increased mortality but is also associated with increased hospitalizations, greater number of emergency department visits, nonadherence to treatments, higher health care utilization costs and decreased quality of life.[7,9,10,12-14] Studies have reported that people with both schizophrenia and type 2 diabetes have worse cognitive deficit than schizophrenia without diabetes or diabetes alone, which can significantly impede their social rehabilitation and lead to poor clinical and functional outcomes.[15,16]

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Table 1. Search Terms and Subject Headings in PubMed Format (Modified in Other Search Engines).

Search	Query
#1	neighborhood [Title/Abstract] OR neighbourhood [Title/Abstract] OR "residence characteristics" [Title/Abstract] OR community [Title/Abstract] OR "small area" [Title/Abstract] OR context [Title/Abstract] OR geography [Title/Abstract]
#2	"serious mental illness" [Title/Abstract] OR psychosis [Title/Abstract] OR schizophrenia [Title/Abstract] OR "bipolar disorder " [Title/Abstract] OR "major depression" [Title/Abstract] OR "affective disorders" [Title/Abstract] OR "manic depression" [Title/Abstract]
#3	"type 2 diabetes" [Title/Abstract] OR "type 2 diabetes mellitus" [Title/Abstract] OR "non-insulin dependent diabetes mellitus" [Title/Abstract]
# Final Search	#1 AND #2 AND #3

Numerous studies have established that people who live in disadvantaged environments have worse mental and physical health outcomes than people living in more advantaged areas.[17-25] This phenomenon is commonly referred to as the social gradient of health[26] and is expected to be heightened for people with SMI because of their complex needs.[27] People with mental illness often live in disadvantaged neighborhoods.[28] Lack of adequate health care facilities, decreased access to healthy foods and an unsafe environment in these neighborhoods are often associated with adverse health outcomes such as sedentary life, unhealthy food, choices and obesity,[29-33] which are the major risk factors for T2D.[34-36] It is also proposed that the economic uncertainties associated with deprivation can induce chronic stress, which can result in altered immune system response and activate the hypothalamic-pituitary-adrenal axis leading to diabetes.[10,37] An association between neighborhoods and comorbid diagnosis of SMI and T2D is highly plausible, given what is known about the underlying complex mechanisms that drive these two disorders.

Neighborhood disadvantage has been associated with SMI and T2D.[22-25,38,39] However, only a few studies have examined the associations between neighborhood disadvantage and chronic disease comorbidities.[40,41] There is increasing interest in recent years to address diseases that occur concurrently rather than as separate conditions; that is, are comorbid. Moreover, "syndemics," which is gaining broad recognition in public health literature, also calls for a holistic approach that considers the biological and social interactions of two or more synergistic diseases rather than treating them as separate entities independent of the social context in which they are found.[42]

Given the importance and the degree of public health burden imposed by SMI-T2D comorbidity and the plausibility of an association with neighborhood deprivation, it is imperative to understand the evidence available on the association between neighborhood socioeconomic disadvantage and SMI-T2D comorbidity. Understanding these relationships would be useful in developing evidence based holistic interventions, health care policies and would even help us in designing healthier life spaces. Accordingly, this review aims to synthesize the body of literature examining the association between neighborhood socioeconomic disadvantage and SMI-T2D comorbidity.

Methods

Design

This systematic review followed the Preferred Reporting Items for Systematic review and meta-analysis (PRISMA) format. Research question, inclusion and exclusion criteria and search strategy were developed before the review process based on the PICO (Population, Indicator, Comparison and Outcome) approach. The protocol for this systematic review was registered on PROSPERO (CRD42017083483) and can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=83483.

Search Strategy

Relevant literature was identified through a systematic search of four databases: PubMed, Scopus, Medline, and Web of Science. These databases were selected due to their relative strengths and coverage in medical and social sciences. An initial text search was carried out on PubMed to identify all the possible synonyms of the main concepts and keywords included in the study.

The search strategy consisted of three themes: neighborhoods (neighborhoods, neighbourhoods, residence characteristics, community, small area, context or geography); type 2 diabetes (type 2 diabetes, type 2 diabetes mellitus, non-insulin dependent diabetes mellitus); and serious mental illness (serious mental illness, psychosis, schizophrenia, bipolar disorder, major depression, affective disorders, psychotic disorders) (see Table 1). The reference lists of retrieved articles were hand searched to identify relevant articles that may have been missed in the electronic search. No geographic, date, or study design restrictions were imposed.

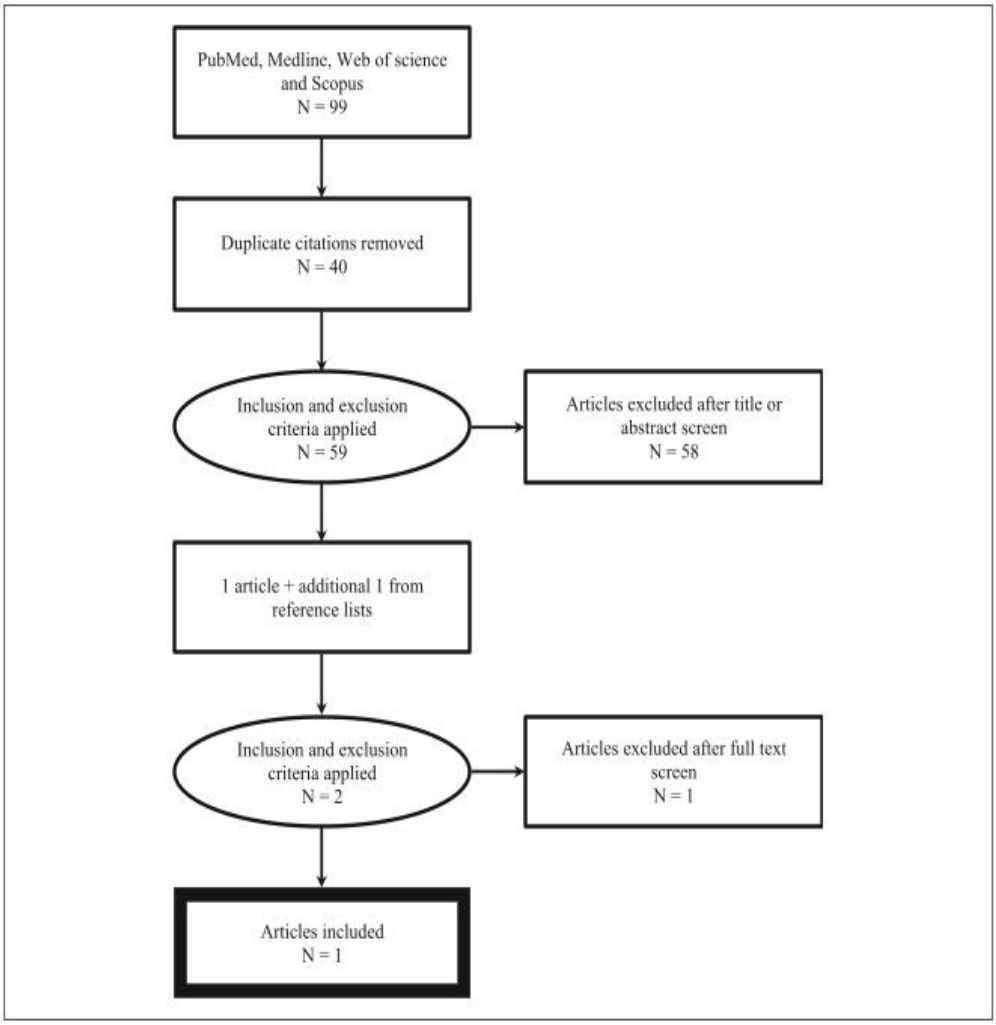

Figure 1. Flowchart of literature search process and the results.

Study Selection

Journal articles that met the following criteria were included in the study: published in English, peer reviewed, quantitative and focusing on the neighborhood disadvantage and SMI-T2D comorbidity. Studies reporting SMI and T2D independently and not as comorbid conditions were excluded from the review. Similarly, studies pertaining to neighborhood features other than disadvantage were also not included.

A 3-step study selection process was employed. In the first step, articles were screened and duplicates were removed. In the second step, the titles and abstracts of remaining articles were reviewed for their eligibility for inclusion. In the third step, eligible articles identified were examined in full for their inclusion in the review. Two reviewers (RW and RT) independently performed all three stages. Study selection procedures are summarized in Figure 1.

Data Extraction

Information extracted from the eligible studies included the following: author, publication date, country of data origin, study population, study design, measures of neighborhood disadvantage, measures of T2D, method of analysis and major findings.

Table 2. Summary of Studies on Neighborhood Disadvantage and Serious Mental Illness–Type 2 Diabetes (SMI-T2D) Comorbidity.

Number	1
Study	Mezuk et al[43] (2013)
Country	Sweden
Sample	336 340 adults
Study design	Longitudinal
SMI measure	Clinically diagnosed major depression from primary care, inpatient, or outpatient registries from January 2001 to December 2007
Neighborhood disadvantage measure	Computed composite index based on education status, income, unemployment, and social welfare assistance
T2D measure	Clinically diagnosed T2D from primary care, inpatient, or outpatient registries, or the use of antidiabetic medications as recorded in primary care/national prescription registries
Method of analysis	Multilevel analysis
Findings	Depression was significantly associated with T2D risk (odds ratio [OR] 1.10, 95% confidence interval [CI] 1.06-1.14). Similar relationship was observed for neighborhood disadvantage (OR high vs low 1.66, 95% CI 1.22-1.34). However, the interaction term between depression and disadvantage was found to be nonsignificant (intraclass correlation 0.013)

Data Analysis

As the focus of this review was to describe the association between neighborhood disadvantage and SMI-T2D comorbidity, the data analysis concentrated on this association. Meta-analysis was thought to be inappropriate because of the heterogeneity expected between the study populations, design and neighborhood measures. Hence, a descriptive review was conducted.

Results

The literature search retrieved a total of 99 potentially relevant records. After excluding 40 duplicates, the remaining 59 articles were screened for their broad eligibility, and a further 58 ineligible articles were excluded. The one remaining article and the additional one retrieved from reference lists were reviewed in full. One article was excluded after full text review leaving one eligible study for inclusion in the review. Study selection outcomes at each stage of the review are summarized in Figure 1.

The one study meeting the selection criteria examined the association between neighborhood disadvantage, major depression and T2D risk among 336 340 adults from Sweden (Table 2). The study relied on identified incident diabetes in those individuals with clinically diagnosed major depression and had a follow-up period of seven years. The measure of neighborhood disadvantage used in the study was a computed index based on four variables: income, education, unemployment and social service assistance. Multilevel logistic regression models were used to assess the relationship between disadvantage and comorbidity.

After accounting for demographic and individual characteristics, such as age, gender, family income, educational attainment and immigration status, the interaction between neighborhood disadvantage and comorbidity risk was found to be nonsignificant ($\beta = 0.01$, 95% confidence interval [CI] −0.06 to 0.06, $P = .573$) indicating that the association between major depression and T2D is similar across different levels of neighborhood disadvantage. Although there was no evidence of synergistic interaction, the attributable risk of T2D due to depression (Diabetes $\text{incidence}_{\text{depression}}$ – Diabetes $\text{incidence}_{\text{without depression}}$) was increased in high deprivation areas (16.4) compared with lower deprivation areas (8.2). The study also highlighted that the individual socioeconomic indicators were not strongly related to T2D risk after controlling for neighborhood factors, indicating the role that contextual factors may play in the development of comorbid association.

Discussion

Our review indicates a paucity of evidence in the research literature investigating the associations between socioeconomic disadvantage and comorbidity of SMI and T2D despite the plausibility of such an association and its implications for health. The only research available reports a nonsignificant association between socioeconomic disadvantage and SMI-T2D cooccurrence.[43] However, the above study focused entirely on major depression, which is often claimed to be under-detected especially in the primary care settings,[44] and did not take into account other forms of SMI such as schizophrenia or bipolar disorder. The study, however, provides indicative evidence of higher attributable risk of T2D in disadvantaged neighborhoods, signaling the focus needed on high deprivation areas in order to reduce the risk of T2D in SMI patients. Furthermore, the study provides an impetus to explore potential neighborhood contextual pathways linking neighborhood deprivation with SMI-T2D comorbidity.

Previous research examining the association between neighborhood disadvantage and T2D risk as an independent condition has established a consistent positive association,

whereby increased neighborhood deprivation is associated with increased T2D risk.[45-47] Research has also shown that multimorbidity is common among populations living in deprived neighborhoods.[40] Although this large cohort study provides only a tentative support for the association between neighborhood socioeconomic disadvantage and SMI-T2D comorbidity, it is consistent with observations showing a high burden of T2D in persons with SMI. More research is needed under different settings and including different forms of SMI to confirm the above results.

Another limitation in the evidence base is that the available study focused mainly on the social aspect of neighborhood disadvantage and used a computed index of disadvantage based on income, education, unemployment and social service assistance and did not focus on the contextual factors of the neighborhoods which might play a significant role. For example, deprived neighborhoods often lack access to fresh produce, and may be dominated by fast food and convenience stores, making the latter the easily available food option.[18] Similarly, deprived neighborhoods might lack an environment conducive to physical activity.[13] The presence of such unobserved moderating or mediating factors might have also contributed to the nonsignificant association between the 2 in the above study.

The lack of a conclusive evidence base makes it difficult to make firm policy recommendations based on our review. Further research is needed to capture the completeness of association between neighborhood deprivation and SMI-T2D comorbidity and the causal pathways linking them. Future research should also focus more on the modifiable contextual or physical aspects of the area that could potentially mediate or moderate the association between deprivation and T2D-SMI comorbidity. Sound knowledge of the factors that are modifiable by interventions will turn out to be more useful and informative for developing policy solutions and interventions.

Conclusions

Research into neighborhood effects on SMI-T2D comorbidity is still in its infancy, and the available evidence inconclusive. This points to an urgent need for attention to the knowledge gap in this important area of population health. Further research is needed to understand the health resource implications of the association between neighborhood deprivation and SMI-T2D comorbidity and the casual pathways linking them. Multilevel study designs can generate more evidence in this direction as it can be useful in analyzing the moderating and mediating processes between neighborhood and individual level variables. Identifying the relationship and connecting processes will help policy makers to develop efficient intervention strategies to curb the syndemics of SMI and T2D.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was conducted with the support of Australian Government Research Training program scholarship and Illawarra Shoalhaven Local Health District–University of Wollongong combined scholarship.

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Author Biographies

Ramya Walsan is a PhD candidate at the School of Medicine, University of Wollongong. Her research proposes to quantify the co-occurence of Serious mental illness – Type 2 diabetes in Illawarra Shoalhaven and to determine its association with neighbourhood factors such as socioeconomic disadvantage.

Andrew Bonney is a general practitioner and Roberta Williams Chair of General Practice at the school of Medicine, University of Wollongong. He is a nationally recognised expert in practice based research with a focus on improving quality and equity in primary care delivery. He's an associate editor for the Australian Journal of Rural Health, Director of Illawarra and Southern Practice Research Network (ISPRN) and Co Director of the Health Impacts Research Cluster (HIRC) within the faculty of Science, Medicine and Health.

Darren J Mayne is a public health epidemiologist with the Illawarra Shoalhaven Local Health District, an honorary fellow at University of Wollongong School of Medicine, and an affiliate researcher with the Illawarra Health and Medical Research Institute. His prinicpal interest is the application of information science methods and spatial statistics to primary, public and population health practice and research.

Nagesh Pai is a professor of Psychaitry at the School of Medicine, University of Wollongong and a senior clinical academic in Psychiatry at the Illawarra Shoalhaven Local Health District (ISLHD). He is an active academic and has been on the RANZCP examinations committee and is a substantial comaparabililty assessor for International Medical graduates in Psychiatry.

Xiaoqi Feng is an associate professor of Epidemiology at University of Wollongong and the co-Director of Population Wellbeing and Environment Research Lab. Dr Feng's teaching and research is multidisciplinary and policy driven, leveraging synergies between public health, geography and economics to enhance understandings of health and wellbeing.

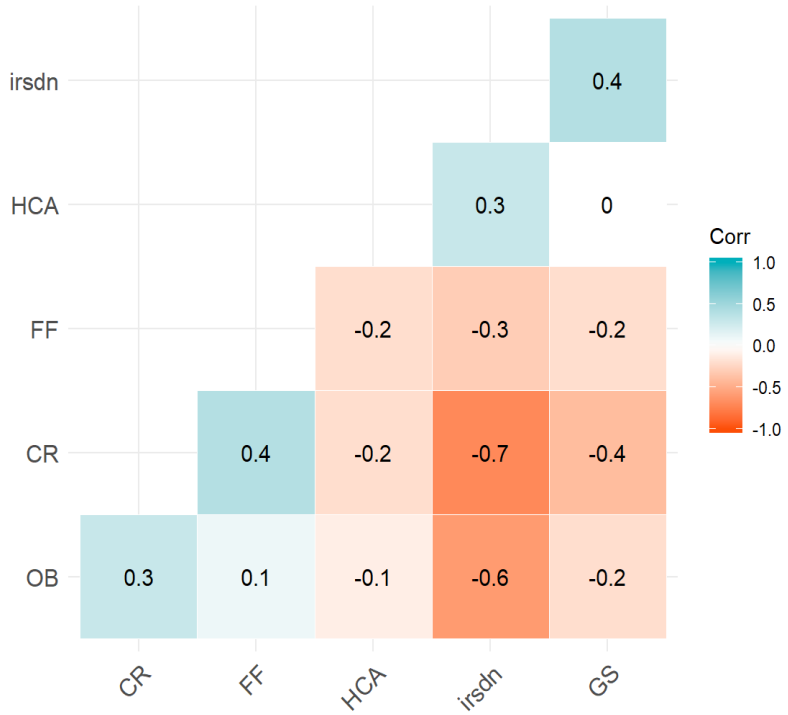
Renin Toms is a PhD candidate at the School of Medicine, University of Wollongong. Her research focuses on epidemiology of chronic disease parameters at regional level, in view of developing a geo enabled visual mapping system to facilitate regional planning activities.

Appendix B: Variance inflation factor calculations and correlation matrix of the neighbourhood variables

Variance inflation calculation for the variables

No	Variable	Variance Inflation factor	DF
1	Age	1.11	1
2	Sex	1.02	1
3	COB	1.13	10
4	IRSD	2.72	1
5	Crime	1.89	1
6	Fast food	1.11	1
7	Health care	1.20	1
8	Green space	1.24	1
9	N. Obesity	1.42	1

Correlation matrix of the neighbourhood variables



Appendix C: R codes used in this study

```
library(readxl)
library(lme4)
library(numDeriv)
library(lmtest)
library(MASS)
library(ggpubr)
library(ggcorrplot)
library(optimx)
library(nloptr)
library(RCurl)
library(dfoptim)
library(car)
```

Importing data set

```
ind <-read_excel("C:/Users/ramya/Desktop/data_new.xlsx")
cdata<-read_excel("C:/Users/ramya/Desktop/study3.xlsx")
```

Factorising and Setting the reference

```
ind$sex <- factor(ind$sex, levels=c("F","M"))
ind$age <- factor(ind$age, levels=c("18-44","45-65","65+"))
ind$irsd <- factor(ind$irsd, levels=c("Q5","Q4","Q3","Q2","Q1"))
ind$COB <-factor(ind$COB,
levels=c("AU","OC","UKI","WE","ECE","NEA","SEA","CSA","MENA","SSA","AM
","UN"))
ind$ssc_code <-factor(ind$ssc_code)
ind$FFQ <-factor(ind$FFQ, levels =c("FF1","FF0"))
ind$CRQ <-factor(ind$CRQ, levels=c("CQ5","CQ4","CQ3","CQ2","CQ1"))
ind$HCQ <-factor(ind$HCQ, levels=c("HC5","HC4","HC3","HC2","HC1"))
ind$GSQ <-factor(ind$GSQ, levels=c("GS5","GS4","GS3","GS2","GS1"))
ind$OBQ <-factor(ind$OBQ, levels=c("OB5","OB4","OB3","OB2","OB1"))
```

```
summary(ind)
```

Checking the distribution of variables

```
a <- density(ind$age_y)
   plot(a, type="n")
   polygon(a, col="red", border="gray")
i <-density(ind$irsdn)
   plot(i, type="n")
   polygon(i, col="red", border="gray")
c <-density(ind$CR)
   plot(c, type="n")
   polygon(c, col="red", border="gray")
   h <-density(ind$HCA)
   plot(h, type="n")
   polygon(h, col="red", border="gray")
o <-density(ind$OB)
   plot(o, type="n")
   polygon(o, col="red", border="gray")
   g <-density(ind$GS)
   plot(g, type="n")
   polygon(g, col="red", border="gray")
f <-density(ind$FF)
   plot(f, type="n")
   polygon(f, col="red", border="gray")
```

Correlation matrix

```
corr <- round(cor(cdata), 1)
ggcorrplot(corr, p.mat = cor_pmat(cdata),
          hc.order = TRUE, type = "lower",
          color = c("#FC4E07", "white", "#00AFBB"),
          outline.col = "white", lab = TRUE)
```

Centering and standardizing

```
ind$age_s <- (ind$age_y - median(ind$age_y)) / sd(ind$age_y )

ind$irsd_s <-(ind$irsdn - median(ind$irsdn)) / sd(ind$irsdn )

ind$CR_s <-(ind$CR - median(ind$CR)) / sd(ind$CR )

ind$HCA_s <-(ind$HCA - median(ind$HCA)) / sd(ind$HCA)

ind$GS_s <-(ind$GS - median(ind$GS)) / sd(ind$GS)

ind$OB_s <-(ind$OB - median(ind$OB)) / sd(ind$OB )

ind$FF_s <-(ind$FF - median(ind$FF)) / sd(ind$FF )
```

Multilevel modelling -Study 2

Null model -Neighbourhood only random effect

```
Model1<-glmer(diabetes_comorbidity ~ (1 | ssc_code), family=binomial("logit"), data=ind)

summary(Model1)

OR1 <- exp(fixef(Model1))

CI1 <- exp(confint(Model1,parm="beta_"))

OR1

CI1
```

Individual only model

```
Model2 <- glmer(diabetes_comorbidity ~  age + sex + COB+(1| ssc_code), family=binomial("logit"), data=ind)
```

Fixing the convergence errors

```
relgrad <- with(Model2@optinfo$derivs,solve(Hessian,gradient))

max(abs(relgrad))


nrow(ind)

length(getME(Model2,"theta"))

length(fixef(Model2))
```

Checking singularity

```
tt <- getME(Model2_sc,"theta")

ll <- getME(Model2_sc,"lower")
```

```
min(tt[ll==0])
```

Double checking gradient calculations

```
derivs1 <- Model2_sc@optinfo$derivs
sc_grad1 <- with(derivs1,solve(Hessian,gradient))
max(abs(sc_grad1))
max(pmin(abs(sc_grad1),abs(derivs1$gradient)))
```

Restart

```
ss <- getME(Model2_sc,c("theta","fixef"))
m2 <- update(Model2_sc,start=ss,control=glmerControl(optCtrl=list(maxfun=2e4)))
```

Trying different optimisers

```
M2 <- update(Model2_sc,start=ss,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
summary(M2)
se <- sqrt(diag(vcov(M2)))
tab2 <- cbind(Est = fixef(M2), LL = fixef(M2) - 1.96 * se, UL = fixef(M2) + 1.96 *
   se)
tab2
exp(tab2)
se.ranef(M2)
```

IRSD only model

```
M3<-glmer(diabetes_comorbidity ~ irsd+(1| ssc_code), family=binomial("logit"),
data=ind,control=glmerControl(optimizer="bobyqa",optCtrl=list(maxfun=2e5)))
summary(M3)
sem3 <- sqrt(diag(vcov(M3)))
tabm3 <- cbind(Est = fixef(M3), LL = fixef(M3) - 1.96 * sem3, UL = fixef(M3) + 1.96
*
   sem3)
tabm3
exp(tabm3)
```

Individual and IRSD variable model

```
Model3 <- glmer(diabetes_comorbidity ~ age+sex+COB+irsd+(1| ssc_code),
family=binomial("logit"),
data=ind,control=glmerControl(optimizer="bobyqa",optCtrl=list(maxfun=2e5)))

summary(Model3)

se3 <- sqrt(diag(vcov(Model3)))

tab3 <- cbind(Est = fixef(Model3), LL = fixef(Model3) - 1.96 * se3, UL =
fixef(Model3) + 1.96 *

   se3)

tab3

exp(tab3)
```

Interaction models

age and irsd interactions

```
Model4 <-glmer(diabetes_comorbidity ~ age+sex+COB+irsd+age*irsd+ (1| ssc_code),
family=binomial("logit"), data=ind,
control=glmerControl(optimizer="bobyqa",optCtrl=list(maxfun=100000)))

summary(Model4)

se4 <- sqrt(diag(vcov(Model4)))

tab3 <- cbind(Est = fixef(Model4), LL = fixef(Model4) - 1.96 * se4, UL =
fixef(Model4) + 1.96 *

   se4)

tab4

exp(tab4)

lrtest(Model4, "age*irsd")
```

sex and irsd interactions

```
Model5 <-glmer(diabetes_comorbidity ~ age+sex+COB+irsd+sex*irsd+ (1| ssc_code),
family=binomial("logit"), data=ind,
control=glmerControl(optimizer="bobyqa",optCtrl=list(maxfun=100000)))

summary(Model5)

se5 <- sqrt(diag(vcov(Model5)))

tab5 <- cbind(Est = fixef(Model5), LL = fixef(Model5) - 1.96 * se5, UL =
fixef(Model5) + 1.96 *

   se5)

tab5
```

```
exp(tab5)

lrtest(Model5, “sex*irsd”)
```

COB and irsd interactions

```
Model6 <-glmer(diabetes_comorbidity ~ age+sex+COB+irsd+COB*irsd+ (1|
ssc_code), family=binomial("logit"), data=ind,
control=glmerControl(optimizer="bobyqa",optCtrl=list(maxfun=100000)))

summary(Model6)

se6 <- sqrt(diag(vcov(Model6)))

tab6 <- cbind(Est = fixef(Model6), LL = fixef(Model6) - 1.96 * se6, UL =
fixef(Model6) + 1.96 *

   se6)

tab6

exp(tab6)

lrtest(Model6, “COB*irsd” )
```

Determine the shrinkage factor for approximating population average effects for model 1 and Model 3

Variance of distribution of random effects from Models 1 and 3

```
tau2 <-c(0.073, 0.05554)

tau2

Shrinkage factor for multiplying cluster specific regression coefficients

shrinkage.factor <-sqrt (1+ (16^2 * 3/(15*pi)^2)*tau2)

shrinkage.factor

k <- 1/sqrt (1+(16^2*3/(15*pi)^2)*tau2)

k
```

Proportion of Opposed Odds ratio for Model 4

```
tau2b<-0.05554

b <-c(0.62689, 0.97760, 1.07133, 1.16383)

POOR <-pnorm (-abs(b/sqrt(2*tau2b)))

POOR
```

Compute ICC (latent variable approach)

```
tau2c <-c (0.09767,0.073, 0.05554)
```

```
ICC <-tau2c/(tau2c+(pi^2)/3)

ICC
```

Median Odds Ratio

```
MOR <-exp(sqrt(2*tau2c)*qnorm(0.75))

MOR
```

Suburb odds ratio

```
getME(Model3,"theta")
```

Multilevel model study 3

Single exposure models (full models only reported)

Area level Crime

```
M3a1 <-
glmer(diabetes_comorbidity~age+sex+COB+irsd+CRQ+(1|ssc_code),family=binomial(
"logit"), data=ind)

M3a <- update(M3a1,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(M3a)

se3a <- sqrt(diag(vcov(M3a)))

tab3a <- cbind(Est = fixef(M3a), LL = fixef(M3a) - 1.96 * se3a, UL = fixef(M3a) +
1.96 *

   se3a)

tab3a

exp(tab3a)

icc3a <-M3a@theta[1]^2/ (M3a@theta[1]^2 + (3.14159^2/3))

icc3a

lrtest(M3a,"CRQ")
```

Health care access

```
M4q <-
glmer(diabetes_comorbidity~age+sex+COB+irsd+HCQ+(1|ssc_code),family=binomial(
"logit"), data=ind)

aa <- allFit(M4q)
```

```
M4uq <- update(M4q,control=glmerControl(optimizer="nlminbwrap",
                    optCtrl=list(maxfun=2e5)))
summary(M4uq)
se4uq <- sqrt(diag(vcov(M4uq)))

tab4uq <- cbind(Est = fixef(M4uq), LL = fixef(M4uq) - 1.96 * se4uq, UL =
fixef(M4uq) + 1.96 *
   se4uq)
tab4uq
exp(tab4uq)
icc4uq <-M4uq@theta[1]^2/ (M4uq@theta[1]^2 + (3.14159^2/3))
icc4uq
lrtest(M4uq,"HCQ")
```

Green space

```
M5q <-
glmer(diabetes_comorbidity~age+sex+COB+irsd+GSQ+(1|ssc_code),family=binomial(
"logit"), data=ind)
M5uq <- update(M5q,control=glmerControl(optimizer="nlminbwrap",
                    optCtrl=list(maxfun=2e5)))
summary(M5uq)
se5uq <- sqrt(diag(vcov(M5uq)))
tab5uq <- cbind(Est = fixef(M5uq), LL = fixef(M5uq) - 1.96 * se5uq, UL =
fixef(M5uq) + 1.96 *
   se5uq)
tab5uq
exp(tab5uq)
lrtest(M5uq,"GSQ")
```

Neighbourhood obesity

```
M64 <-glmer(diabetes_comorbidity ~
OBQ+age+sex+COB+irsd+(1|ssc_code),family=binomial("logit"), data=ind)
M6c <- update(M64,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
```

```
summary(M6c)

se6c <- sqrt(diag(vcov(M6c)))

tab6c <- cbind(Est = fixef(M6c), LL = fixef(M6c) - 1.96 * se6c, UL = fixef(M6c) +
1.96 *

   se6c)

tab6c

exp(tab6c)

lrtest(M6c,"OBQ")
```

Fast food

```
M74 <-glmer(diabetes_comorbidity ~
FFQ+age+sex+COB+irsd+(1|ssc_code),family=binomial("logit"), data=ind)

M7c <- update(M74,control=glmerControl(optimizer="Nelder_Mead",

                    optCtrl=list(maxfun=2e5)))

summary(M7c)

se7c <- sqrt(diag(vcov(M7c)))

tab7c <- cbind(Est = fixef(M7c), LL = fixef(M7c) - 1.96 * se7c, UL = fixef(M7c) +
1.96 *

   se7c)

tab7c

exp(tab7c)

lrtest(M7c,"FFQ")
```

Multivariable models

```
M <- glmer(diabetes_comorbidity ~
age+sex+COB+irsd+CRQ+HCQ+GSQ+OBQ+FFQ+(1|ssc_code),family=binomial("lo
git"), data=ind)

Mu <- update(M,control=glmerControl(optimizer="Nelder_Mead",

                    optCtrl=list(maxfun=2e5)))


summary(Mu)

seu <- sqrt(diag(vcov(Mu)))
```

```
tabu<- cbind(Est = fixef(Mu), LL = fixef(Mu) - 1.96 * se7c, UL = fixef(Mu) + 1.96 *
   seu)
tabu
exp(tabu)
icc <-Mu@theta[1]^2/ (Mu@theta[1]^2 + (3.14159^2/3))
icc
lrtest( Mu, “CRQ”)
lrtest(Mu, “HCQ”)
lrtest(Mu, “OBQ”)
lrtest(Mu, “GSQ”)
lrtest(Mu, “FFQ”)
```

Individual and neighbourhood Interactions

area level crime and age

```
M1 <-glmer(diabetes_comorbidity~ age+sex+COB+irsd+CRQ+
HCQ+GSQ+OBQ+FFQ+ (1|ssc_code)+CRQ:age,family=binomial("logit"), data=ind)
Mh <- update(M1,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
summary(Mh)
seh <- sqrt(diag(vcov(Mh)))
tabh <- cbind(Est = fixef(Mh), LL = fixef(Mh) - 1.96 * seh, UL = fixef(Mh) + 1.96 *
   seh)
tabh
exp(tabh)
Anova(Mh)
```

area level crime and sex

```
M2 <-glmer(diabetes_comorbidity~ age+sex+COB+CRQ+ HCQ+GSQ+OBQ+FFQ
+(1|ssc_code)+CRQ:sex,family=binomial("logit"), data=ind)
M2u <- update(M2,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
summary(M2u)
```

```
s2 <- sqrt(diag(vcov(M2u)))
tab2 <- cbind(Est = fixef(M2u), LL = fixef(M2u) - 1.96 * s2, UL = fixef(M2u) + 1.96 *
   s2)
tab2
exp(tab2)
Anova(M2u)
```

area level crime and COB

```
M3 <-glmer(diabetes_comorbidity~ age+sex+COB+CRQ+ HCQ+GSQ+OBQ+FFQ
+(1|ssc_code)+ CRQ:COB,family=binomial("logit"), data=ind)
M3u <- update(M3,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
summary(M3u)
s3 <- sqrt(diag(vcov(M3u)))
tab3 <- cbind(Est = fixef(M3u), LL = fixef(M3u) - 1.96 * s3, UL = fixef(M3u) + 1.96 *
   s3)
tab3
exp(tab3)
Anova(M3u)
```

Health care access and age

```
M4 <-glmer(diabetes_comorbidity~ age+sex+COB+CRQ+ HCQ+GSQ+OBQ+FFQ
+(1|ssc_code)+ HCQ:age,family=binomial("logit"), data=ind)
M4u <- update(M4,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
summary(M4u)
s4 <- sqrt(diag(vcov(M4u)))
tab4 <- cbind(Est = fixef(M4u), LL = fixef(M4u) - 1.96 * s4, UL = fixef(M4u) + 1.96 *
   s4)
tab4
exp(tab4)
Anova(M4u)
```

Health care access and sex

```
M5 <-glmer(diabetes_comorbidity~
age+sex+COB+HCQ+CRQ+OBQ+FFQ+(1|ssc_code)+
HCQ:sex,family=binomial("logit"), data=ind)

M5u <- update(M5,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(M5u)

s5<- sqrt(diag(vcov(M5u)))

tab5 <- cbind(Est = fixef(M5u), LL = fixef(M5u) - 1.96 * s5, UL = fixef(M5u) + 1.96 *

   s5)

tab5

exp(tab5)

Anova(M5u)
```

Health care access and COB

```
M6 <-glmer(diabetes_comorbidity~ age+sex+COB+HCQ+ CRQ+OBQ+FFQ+(
(1|ssc_code)+ HCQ:COB,family=binomial("logit"), data=ind)

M6u <- update(M6,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(M6u)

s6<- sqrt(diag(vcov(M6u)))

tab6 <- cbind(Est = fixef(M6u), LL = fixef(M6u) - 1.96 * s6, UL = fixef(M6u) + 1.96 *

   s6)

tab6

exp(tab6)

Anova(M6u)
```

Green space and age

```
M7 <-glmer(diabetes_comorbidity~
age+sex+COB+GSQ+CRQ+HCQ+OBQ+FFQ+(1|ssc_code)+
GSQ:age,family=binomial("logit"), data=ind)

M7u <- update(M7,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(M7u)
```

```
s7<- sqrt(diag(vcov(M7u)))

tab7 <- cbind(Est = fixef(M7u), LL = fixef(M7u) - 1.96 * s7, UL = fixef(M7u) + 1.96 *
   s7)

tab7

exp(tab7)

Anova(M7u)
```

Green space and sex

```
M8 <-glmer(diabetes_comorbidity~ age+sex+COB+GSQ+ CRQ+HCQ+OBQ+FFQ+
(1|ssc_code)+ GSQ:sex,family=binomial("logit"), data=ind)

M8u <- update(M8,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))

summary(M8u)

s8<- sqrt(diag(vcov(M8u)))

tab8 <- cbind(Est = fixef(M8u), LL = fixef(M8u) - 1.96 * s8, UL = fixef(M8u) + 1.96 *
   s8)

tab8

exp(tab8)

Anova(M8u)
```

Green space and COB

```
M9 <-glmer(diabetes_comorbidity~ age+sex+COB+GSQ+ CRQ+HCQ+OBQ+FFQ+
(1|ssc_code)+ GSQ:COB,family=binomial("logit"), data=ind)

M9u <- update(M9,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))

summary(M9u)

s9<- sqrt(diag(vcov(M9u)))

tab9 <- cbind(Est = fixef(M9u), LL = fixef(M9u) - 1.96 * s9, UL = fixef(M9u) + 1.96 *
   s9)

tab9

exp(tab9)

Anova(M9u)
```

Neighbourhood obesity and age

```
M10 <-glmer(diabetes_comorbidity~
age+sex+COB+OBQ+CRQ+HCQ+GSQ+FFQ+(1|ssc_code)+
OBQ:age,family=binomial("logit"), data=ind)

M10u <- update(M10,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(M10u)

s10<- sqrt(diag(vcov(M10u)))

tab10 <- cbind(Est = fixef(M10u), LL = fixef(M10u) - 1.96 * s10, UL = fixef(M10u) +
1.96 *

   s10)

tab10

exp(tab10)

Anova(M10u)
```

Neighbourhood obesity and sex

```
M11 <-glmer(diabetes_comorbidity~ age+sex+COB+OBQ+ CRQ+HCQ+GSQ+FFQ+
(1|ssc_code)+ OBQ:sex,family=binomial("logit"), data=ind)

M11u <- update(M11,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(M11u)

s11<- sqrt(diag(vcov(M11u)))

tab11 <- cbind(Est = fixef(M11u), LL = fixef(M11u) - 1.96 * s11, UL = fixef(M11u) +
1.96 *

   s11)

tab11

exp(tab11)

Anova(M11u)
```

Neighbourhood obesity and COB

```
M12 <-glmer(diabetes_comorbidity~ age+sex+COB+OBQ+ CRQ+HCQ+GSQ+FFQ+
(1|ssc_code)+ OBQ:COB,family=binomial("logit"), data=ind)

M12u <- update(M12,control=glmerControl(optimizer="bobyqa",
```

```
                optCtrl=list(maxfun=2e5)))
summary(M12u)
s12<- sqrt(diag(vcov(M12u)))
tab12 <- cbind(Est = fixef(M12u), LL = fixef(M12u) - 1.96 * s12, UL = fixef(M12u) +
1.96 *
   s12)
tab12
exp(tab12)
Anova(M12u)
```

Fast food and age

```
M13 <-glmer(diabetes_comorbidity~
age+sex+COB+FFQ+CRQ+HCQ+OBQ+GSQ+(1|ssc_code)+
FFQ:age,family=binomial("logit"), data=ind)
M13u <- update(M13,control=glmerControl(optimizer="bobyqa",
                optCtrl=list(maxfun=2e5)))
summary(M13u)
s13<- sqrt(diag(vcov(M13u)))
tab13 <- cbind(Est = fixef(M13u), LL = fixef(M13u) - 1.96 * s13, UL = fixef(M13u) +
1.96 *
   s13)
tab13
exp(tab13)
Anova(M13u)
```

Fast food and sex

```
M14 <-glmer(diabetes_comorbidity~ age+sex+COB+FFQ+ CRQ+HCQ+OBQ+GSQ+
(1|ssc_code)+ FFQ:sex,family=binomial("logit"), data=ind)
M14u <- update(M14,control=glmerControl(optimizer="bobyqa",
                optCtrl=list(maxfun=2e5)))
summary(M14u)


s14<- sqrt(diag(vcov(M14u)))
```

```
tab14 <- cbind(Est = fixef(M14u), LL = fixef(M14u) - 1.96 * s14, UL = fixef(M14u) + 1.96 *
   s14)
tab14
exp(tab14)
Anova(M14u)
```

Fast food and country of birth

```
M15 <-glmer(diabetes_comorbidity~ age+sex+COB+FFQ+ CRQ+HCQ+OBQ+GSQ+ (1|ssc_code)+ FFQ:COB,family=binomial("logit"), data=ind)
M15u <- update(M15,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
summary(M15u)
s15<- sqrt(diag(vcov(M15u)))
tab15 <- cbind(Est = fixef(M15u), LL = fixef(M15u) - 1.96 * s15, UL = fixef(M15u) + 1.96 *
   s15)
tab15
exp(tab15)
Anova(M15u)
```

Neighbourhood and neighbourhood interactions

Area level crime and IRSD

```
N1 <-glmer(diabetes_comorbidity~ age+sex+COB+CRQ+irsd+ HCQ+OBQ+GSQ+FFQ+(1|ssc_code)+CRQ:irsd,family=binomial("logit"), data=ind)
N1u <- update(N1,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
summary(N1u)
s1 <- sqrt(diag(vcov(N1u)))
t1 <- cbind(Est = fixef(N1u), LL = fixef(N1u) - 1.96 * s1, UL = fixef(N1u) + 1.96 *
   s1)
t1
exp(t1)
Anova(N1u)
```

health care access and irsd

```
N2 <-glmer(diabetes_comorbidity~
age+sex+COB+HCQ+irsd+CRQ+OBQ+GSQ+FFQ+
(1|ssc_code)+HCQ:irsd,family=binomial("logit"), data=ind)

N2u <- update(N2,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(N2u)

s2 <- sqrt(diag(vcov(N2u)))

t2 <- cbind(Est = fixef(N2u), LL = fixef(N2u) - 1.96 * s2, UL = fixef(N2u) + 1.96 *

   s2)

t2

exp(t2)

Anova(N2u)
```

Green space and irsd

```
N3 <-glmer(diabetes_comorbidity~
age+sex+COB+GSQ+irsd+CRQ+HCQ+OBQ+FFQ+
(1|ssc_code)+GSQ:irsd,family=binomial("logit"), data=ind)

N3u <- update(N3,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(N3u)

s3 <- sqrt(diag(vcov(N3u)))

t3 <- cbind(Est = fixef(N3u), LL = fixef(N3u) - 1.96 * s3, UL = fixef(N3u) + 1.96 *

   s3)

t3

exp(t3)

Anova(N3u)
```

neighbourhood obesity and irsd

```
N4 <-glmer(diabetes_comorbidity~ age+sex+COB+OBQ+irsd+
CRQ+HCQ+OBQ+FFQ+(1|ssc_code)+OBQ:irsd,family=binomial("logit"), data=ind)

N4u <- update(N4,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))
```

```
summary(N4u)
s4 <- sqrt(diag(vcov(N4u)))
t4 <- cbind(Est = fixef(N4u), LL = fixef(N4u) - 1.96 * s4, UL = fixef(N4u) + 1.96 *
   s4)


t4
exp(t4)
Anova(N4u)
```

fast food and irsd

```
N5 <-glmer(diabetes_comorbidity~ age+sex+COB+FFQ+irsd+
CRQ+HCQ+OBQ+GSQ+(1|ssc_code)+FFQ:irsd,family=binomial("logit"), data=ind)
N5u <- update(N5,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
summary(N5u)
s5 <- sqrt(diag(vcov(N5u)))
t5 <- cbind(Est = fixef(N5u), LL = fixef(N5u) - 1.96 * s5, UL = fixef(N5u) + 1.96 *
   s5)
t5
exp(t5)
Anova(N5u)
```

Area level crime and health care access

```
N6 <-glmer(diabetes_comorbidity~ age+sex+COB+HCQ+CRQ+
OBQ+FFQ+GSQ+irsd+(1|ssc_code)+HCQ:CRQ,family=binomial("logit"), data=ind)
N6u <- update(N6,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
summary(N6u)
s6 <- sqrt(diag(vcov(N6u)))
t6 <- cbind(Est = fixef(N6u), LL = fixef(N6u) - 1.96 * s6, UL = fixef(N6u) + 1.96 *
   s6)
t6
exp(t6)
```

```
Anova(N6u)
```

Area level crime and obesity

```
N7 <-glmer(diabetes_comorbidity~ age+sex+COB+OBQ+CRQ+
HCQ+GSQ+FFQ+irsd+(1|ssc_code)+OBQ:CRQ,family=binomial("logit"), data=ind)

N7u <- update(N7,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))


summary(N7u)

s7 <- sqrt(diag(vcov(N7u)))

t7 <- cbind(Est = fixef(N7u), LL = fixef(N7u) - 1.96 * s7, UL = fixef(N7u) + 1.96 *
   s7)

t7

exp(t7)

Anova(N7u)
```

Area level crime and green space

```
N8 <-glmer(diabetes_comorbidity~ age+sex+COB+GSQ+CRQ+
HCQ+OBQ+FFQ+irsd+(1|ssc_code)+GSQ:CRQ,family=binomial("logit"), data=ind)

N8u <- update(N8,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))

summary(N8u)

s8 <- sqrt(diag(vcov(N8u)))

t8 <- cbind(Est = fixef(N8u), LL = fixef(N8u) - 1.96 * s8, UL = fixef(N8u) + 1.96 *
   s8)

t8

exp(t8)

Anova(N8u)
```

Area level crime and fast food

```
N9 <-glmer(diabetes_comorbidity~ age+sex+COB+FFQ+CRQ+
HCQ+OBQ+GSQ+irsd+(1|ssc_code)+FFQ:CRQ,family=binomial("logit"), data=ind)

N9u <- update(N9,control=glmerControl(optimizer="bobyqa",
                    optCtrl=list(maxfun=2e5)))
```

```
summary(N9u)

s9 <- sqrt(diag(vcov(N9u)))

t9<- cbind(Est = fixef(N9u), LL = fixef(N9u) - 1.96 * s9, UL = fixef(N9u) + 1.96 *

   s9)

t9

exp(t9)

Anova(N9u)
```

health care and green space

```
N10 <-glmer(diabetes_comorbidity~ age+sex+COB+HCQ+GSQ+
CRQ+OBQ+FFQ+irsd+(1|ssc_code)+HCQ:GSQ,family=binomial("logit"), data=ind)

N10u <- update(N10,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(N10u)

s10 <- sqrt(diag(vcov(N10u)))

t10<- cbind(Est = fixef(N10u), LL = fixef(N10u) - 1.96 * s10, UL = fixef(N10u) + 1.96
*

   s10)

t10

exp(t10)

Anova(N10u)
```

health care and obesity

```
N11 <-glmer(diabetes_comorbidity~ age+sex+COB+HCQ+OBQ+
CRQ+GSQ+FFQ+irsd+(1|ssc_code)+HCQ:OBQ,family=binomial("logit"), data=ind)

N11u <- update(N11,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(N11u)

s11 <- sqrt(diag(vcov(N11u)))

t11<- cbind(Est = fixef(N11u), LL = fixef(N11u) - 1.96 * s11, UL = fixef(N11u) + 1.96
*

   s11)

t11
```

```
exp(t11)

Anova(N11u)
```

Health care and Fast food

```
N12 <-glmer(diabetes_comorbidity~
age+sex+COB+HCQ+FFQ+CRQ+OBQ+GSQ+irsd+
(1|ssc_code)+HCQ:FFQ,family=binomial("logit"), data=ind)

N12u <- update(N12,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(N12u)

s12 <- sqrt(diag(vcov(N12u)))

t12<- cbind(Est = fixef(N12u), LL = fixef(N12u) - 1.96 * s12, UL = fixef(N12u) + 1.96
*

   s12)

t12

exp(t12)

Anova(N12u)
```

Green space and obesity

```
N13 <-glmer(diabetes_comorbidity~ age+sex+COB+GSQ+OBQ+
CRQ+HCQ+FFQ+irsd+(1|ssc_code)+GSQ:OBQ,family=binomial("logit"), data=ind)

N13u <- update(N13,control=glmerControl(optimizer="bobyqa",

                    optCtrl=list(maxfun=2e5)))

summary(N13u)

s13 <- sqrt(diag(vcov(N13u)))

t13<- cbind(Est = fixef(N13u), LL = fixef(N13u) - 1.96 * s13, UL = fixef(N13u) + 1.96
*

   s13)

t13

exp(t13)

Anova(N13u)
```

Green space and fast food

```
N14 <-glmer(diabetes_comorbidity~ age+sex+COB+GSQ+FFQ+
CRQ+HCQ+OBQ+irsd+(1|ssc_code)+GSQ:FFQ,family=binomial("logit"), data=ind)
```

```
N14u <- update(N14,control=glmerControl(optimizer="bobyqa",
                        optCtrl=list(maxfun=2e5)))
summary(N14u)
s14 <- sqrt(diag(vcov(N14u)))
t14<- cbind(Est = fixef(N14u), LL = fixef(N14u) - 1.96 * s14, UL = fixef(N14u) + 1.96
*
   s14)
t14
exp(t14)
Anova(N14u)
```

Neighbourhood obesity and fast food

```
N15 <-glmer(diabetes_comorbidity~ age+sex+COB+OBQ+FFQ+
CRQ+HCQ+GSQ+irsd+(1|ssc_code)+OBQ:FFQ,family=binomial("logit"), data=ind)
N15u <- update(N15,control=glmerControl(optimizer="bobyqa",
                        optCtrl=list(maxfun=2e5)))


summary(N15u)
s15 <- sqrt(diag(vcov(N15u)))
t15<- cbind(Est = fixef(N15u), LL = fixef(N15u) - 1.96 * s15, UL = fixef(N15u) + 1.96
*
   s15)
t15
exp(t15)
Anova(N15u)
```

Appendix D: Published Study 1 article

PLOS ONE

RESEARCH ARTICLE

Exploring the geography of serious mental illness and type 2 diabetes comorbidity in Illawarra—Shoalhaven, Australia (2010 -2017)

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OPEN ACCESS

Citation: Walsan R, Mayne DJ, Pai N, Feng X, Bonney A (2019) Exploring the geography of serious mental illness and type 2 diabetes comorbidity in Illawarra—Shoalhaven, Australia (2010 -2017). PLoS ONE 14(12): e0225992. https://doi.org/10.1371/journal.pone.0225992

Editor: Mohammad Ali, Johns Hopkins Bloomberg School of Public Health, UNITED STATES

Received: May 6, 2019

Accepted: November 18, 2019

Published: December 5, 2019

Data Availability Statement: The IHIP and SIMLR data used in this study are bound by strict data governance and sharing agreements and hence data sharing is restricted. However, details on accessing these data are available on the Centre for Health Research Illawarra Shoalhaven Population (https://ahsri.uow.edu.au/chrisp/ihip-data) and Illawarra and Southern Practice Research Network (https://smah.uow.edu.au/isprn/partner-projects) websites.

Abstract

Objectives

The primary aim of this study was to describe the geography of serious mental illness (SMI)–type 2 diabetes comorbidity (T2D) in the Illawarra-Shoalhaven region of NSW, Australia. The Secondary objective was to determine the geographic concordance if any, between the comorbidity and the single diagnosis of SMI and diabetes.

Methods

Spatial analytical techniques were applied to clinical data to explore the above objectives. The geographic variation in comorbidity was determined by Moran's I at the global level and the local clusters of significance were determined by Local Moran's I and spatial scan statistic. Choropleth hotspot maps and spatial scan statistics were generated to assess the geographic convergence of SMI, diabetes and their comorbidity. Additionally, we used bivariate LISA (Local Indicators of Spatial Association) and multivariate spatial scan to identify coincident areas with higher rates of both SMI and T2D.

Results

The study identified significant geographic variation in the distribution of SMI–T2D comorbidity in Illawarra Shoalhaven. Consistently higher burden of comorbidity was observed in some urban suburbs surrounding the major metropolitan city. Comparison of comorbidity hotspots with the hotspots of single diagnosis SMI and T2D further revealed a geographic concordance of high-risk areas again in the urban areas outside the major metropolitan city.

Research design and methods

Study area and population

This cross sectional study was carried out in the Illawarra and Shoalhaven regions of New South Wales, Australia, which had an estimated resident population of 368,604 people at the time of the 2011 Australian Census of Population and Housing[21]. Serious mental illness and diabetes comorbidity data for the period of 2010 to 2017 were obtained from the Illawarra Health Information Platform (IHIP), which is a research partnership established between Illawarra Shoalhaven Local Health District (ISLHD) and University of Wollongong for the purpose of providing ISLHD health service data to researchers. Community-derived diabetes data (without reference to comorbidities), were retrieved from the Southern IML Research (SIMLR) study database for the period of 2010 to 2014. SIMLR is a longitudinal, community-derived near-census database consisting of routinely collected pathology results for residents 18 years and over in Illawarra Shoalhaven[14]. All the data used in this study were deidentified prior to extraction, consistent with the requirements of the Privacy Act 1988 (Cth) and Health Records and Information Privacy Act 2002 (NSW). Residential suburbs were the smallest geographical units at which health service data were available and were used as the spatial units of analysis. Information on the population of the region by age groups and gender was obtained from the 2011 Australian Census of population and housing[21]. To display and analyse the geographic distribution of SMI, T2D and their comorbidity, a base map of the Australian suburbs 2011 digital boundaries from Australian Bureau of Statistics was used. This study was approved by The University of Wollongong and Illawarra Shoalhaven Local Health District Human Research Ethics Committee (protocol number 2017/428).

Study sample

Serious mental illness in our study was defined as a primary or secondary diagnosis of SMI from the inpatient records of ISLHD. Data extraction was carried out by means of International Classification of Diseases (ICD) 10 codes (Table 1). Comorbidity was defined as having a T2D stay diagnosis code (ICD code E11) in people with serious mental illness recorded in the ISLHD data. Comorbidity details were extracted as either present or absent along with each of the SMI records. The community-derived diabetes sample, consisted of individuals with at least one HbA1c test between 2010 and 2014 and an HbA1c result $\geq$ 6.5% or plasma glucose levels $\geq$7.0mmol/L within 12 months of an HbA1c test, consistent with thresholds used in the Australian National Health Measures Survey [22]. Data analysis was restricted to individuals 18 years and over.

Statistical analysis

We calculated the relative risk of SMI-T2D comorbidity for each of the 167 suburbs in the Illawarra Shoalhaven region by computing the ratio of observed to the expected counts. The

Table 1. SMI diagnosis groups and ICD 10 codes included in the study.

Diagnosis	ICD 10 codes
Schizophrenia	F20
Other non-affective psychosis	F22 –F29
Bipolar disorder	F30, F31
Major depression	F32, F33
Other affective disorders	F34, F39

https://doi.org/10.1371/journal.pone.0225992.t001

expected number of cases was calculated by indirect standardisation and was obtained by multiplying age-sex stratified population in each suburb by the age-sex stratified prevalence across the entire study area. Expected counts for males and females aged 18–34, 35–49, 50–64 and 65+years were calculated separately and were then aggregated within suburbs to create an aggregated denominator for the relative risk. Data over the entire study period (2010–2017) were combined to ensure sufficient counts. The population profile of the study area had remained relatively similar during these time period[21]. Suburbs with expected counts of zero (n = 5) were merged with the neighbouring suburbs for further analysis. Large variance in relative risks was observed due to sparse comorbidity counts and the heterogeneous population density in the area. To address this issue, relative risk data were smoothed using the Empirical Bayes smoothing technique recommended by Anselin and Koschinsky to shrink and stabilise the rates towards the global mean of the whole study region[23].

Global Moran's I was used to investigate spatial autocorrelation or clustering in the raw estimates[24]. Moran's I statistic ranges between -1 and 1, with a value of zero indicating complete spatial randomness; a positive value indicating positive spatial autocorrelation; and a negative value indicating negative spatial autocorrelation[24]. Local Indicator of Spatial Association (LISA) and spatial scan statistics were used to identify the location of comorbidity clusters. These two spatial analytical techniques were adopted simultaneously to complement the findings and to provide more intuitive results [25]. LISA, often known as Local Moran's I, was used to detect the significant clusters of higher and lower relative risks of comorbidity[24]. High-high clusters are areas of significantly high rates surrounded by other areas of significantly higher rates, and low-low clusters represents areas with lower risks surrounded by other areas of lower values[26,27].

Spatial scan statistics works by imposing circular scanning windows of varying radii, which gradually moves over the study area evaluating the likelihood ratios of all potential clusters using a user defined maximum percentage of population at risk[28], which in this analysis was set at a default maximum spatial cluster size of $\leq$ 50%[29]. We employed a purely spatial retrospective scan using the discrete Poisson model, where by the number of events is assumed to be Poisson distributed [28]. The input data for this model consisted of the observed and the expected comorbidity counts. The 'no geographic overlap' criterion was used to report the clusters and the p values calculated were two tailed.

In order to compare the geographic concordance of SMI-T2D comorbidity with the single diagnosis of SMI and diabetes in the general population (Gen-DM), relative risk maps, LISA maps and spatial scan statistics were generated for SMI and Gen-DM following the same procedures as the comorbidity map. Additionally, we used bivariate LISA[26,27] and multivariate spatial scan[28] statistics to test the association between SMI and Gen-DM and to map their associations at suburb level. The LISA bivariate statistic indicates how observations of a variable (SMI) in a certain suburb are associated with the observations of a different variable (Gen-DM) in the adjacent suburb. In our case, high-high clusters will indicate coincident areas of high rates of SMI and Gen-DM and low-low clusters will be the areas of coincident low rates of SMI and Gen-DM. Multivariate spatial scan identifies spatial clusters with higher and lower rates for both SMI and Gen-DM by simultaneously searching for and evaluating clusters within the two datasets. The likelihood ratio for each data set is summed up to determine the likelihood ratio for that particular window[28].

The statistical significance of Global Moran's I, Local Moran's I, Spatial scan and bivariate LISA were evaluated under the complete spatial randomness assumptions using 9999 Monte Carlo simulations and a significance level of 0.05[30]. Benjamini Hochberg correction was applied to control for false discovery rates in LISA and Bivariate LISA statistics[31].

Software

We used Geo Da [27] for Empirical Bayes Smoothing and spatial analysis, SaTScan for univariate and multivariate spatial scan statistics[28], R for descriptive analysis [32] and Arc GIS 10.5 for mapping[33].

Results

Sample description

A total of 4165 unduplicated records were extracted with an SMI diagnosis between 1 January 2010 and 31 December 2017. Individuals residing outside the Illawarra Shoalhaven area (n = 50) and records with no suburb information (n = 283) were excluded from our analysis (n = 341, 8.2%) resulting in a final SMI sample of 3824 people. Of these, 463 (12.1%) had a T2D comorbidity. The community-derived diabetes sample for the region consisted of 13142 unique individuals. The distribution of SMI, diabetes and their comorbidity in the Illawarra and Shoalhaven is described in Table 2. The median age of the comorbidity subgroup was 58 years (range = 18–92 years). The gender distribution was approximately equal with females accounting for 52.9% of the sample. Higher comorbidity prevalence was observed in older adults above 50 years of age.

Spatial distribution of SMI -T2D comorbidity

The geographic distribution of smoothed relative risks for SMI-T2D comorbidity in the Illawarra and Shoalhaven is depicted in Fig 1. Moran's I revealed a positive global spatial autocorrelation for SMI-T2D relative risk (Moran's I = 0.1155, p = 0.0361) indicating that suburbs with similar SMI- T2D risk are clustered geographically. Fig 2 demonstrates the results of the application of LISA and spatial scan statistics to the SMI-T2D comorbidity risk by suburbs.

LISA analysis identified twelve (12) significant high-high clusters (hotspots) and four (4) low-low clusters (cold spots), that became non-significant after correcting for multiple comparisons using the Benjamini–Hochberg FDR procedure. However, there was a strong correspondence between uncorrected LISA and spatial scan analysis in identifying a hotspot south of major metropolitan area as shown in Fig 2. The spatial scan statistics using a maximum cluster size of ≤50% of total population identified one significant high rate cluster of

Table 2. Distribution of serious mental illness, type 2 diabetes and their comorbidity in Illawarra Shoalhaven (2010–2017).

Demographic characteristics	Serious mental illness	Diabetes	Serious mental illness -type 2 diabetes comorbidity
Total	**3824**	**13142**	**463**
Sex			
Male n (%)	1977 (51.7)	7248 (55.2)	218 (47.1)
Female n (%)	1847 (48.3)	5894 (44.8)	245 (52.9)
Age (Years)			
18–34 n (%)	1132 (29.6)	189 (1.4)	27 (5.8)
35–49 n (%)	1220 (31.8)	733 (5.6)	108 (23.3)
50–64 n (%)	820 (21.4)	3294 (25.1)	150 (32.4)
65+ n (%)	652 (17.1)	8926 (67.9)	178 (38.4)

https://doi.org/10.1371/journal.pone.0225992.t002

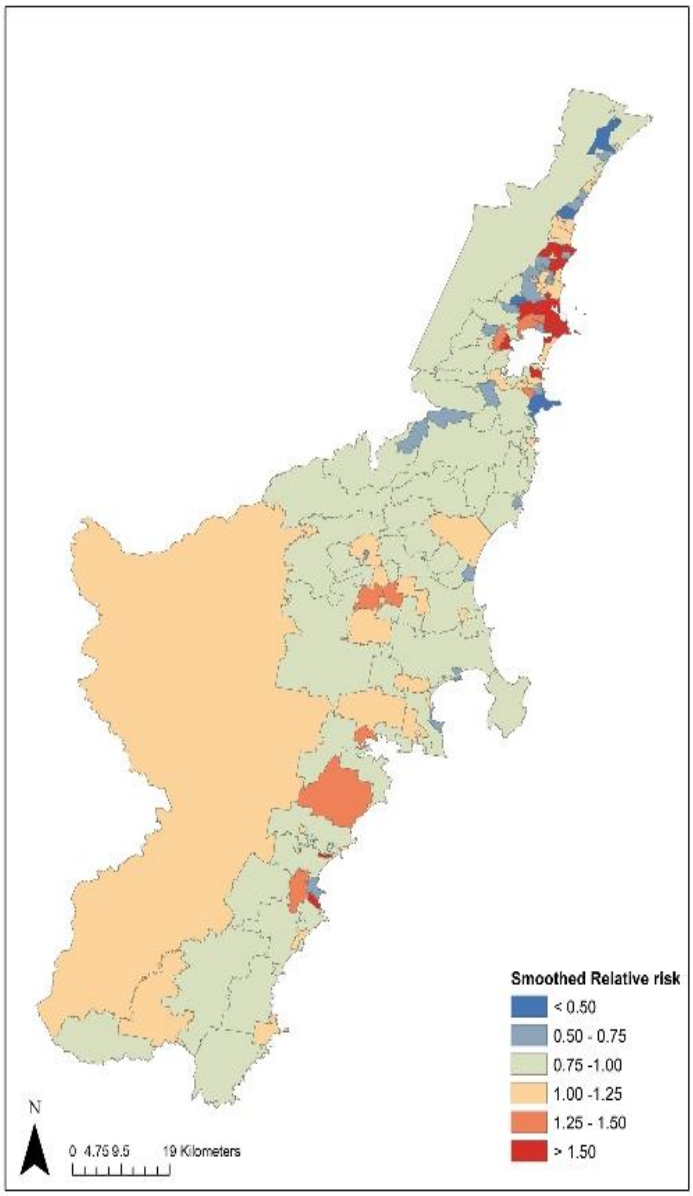

Fig 1. Smoothed relative risk of SMI-T2D comorbidity in the Illawarra Shoalhaven (2010–2017).

https://doi.org/10.1371/journal.pone.0225992.g001

SMI-T2D comorbidity in the suburbs south of major metropolitan city centre (Fig 2). The high rate cluster identified comprised of 23 urban suburbs and had a relative risk of 1.80 ($p < 0.001$). The number of observed comorbidity cases in this cluster was 110, compared to 68 expected cases. The identified high rate cluster contained 14.2% of the total population in

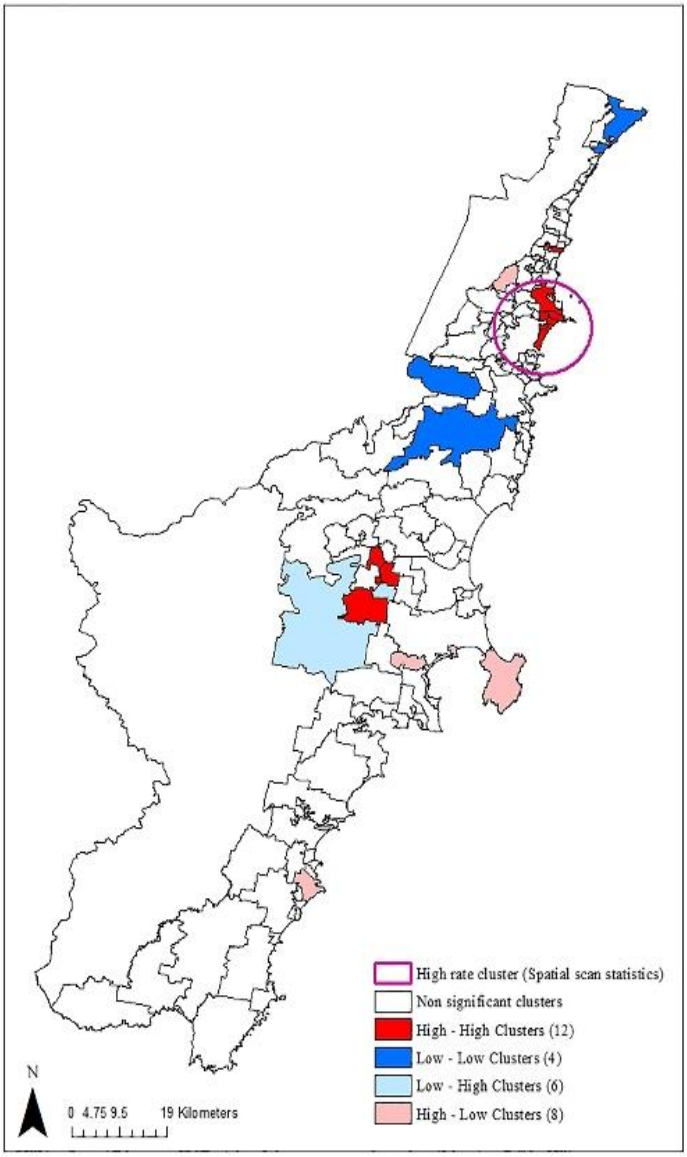

Fig 2. Local Moran's I and spatial scan statistics calculated for SMI-T2D comorbidity in Illawarra—Shoalhaven (2010–2017).

https://doi.org/10.1371/journal.pone.0225992.g002

the Illawarra Shoalhaven. No significant low rate clusters were detected by spatial scan. Six urban suburbs south of major metropolitan city were identified as high-risk areas for SMI-T2D comorbidity as they consistently appeared in both LISA and spatial scan statistics as a high rate cluster.

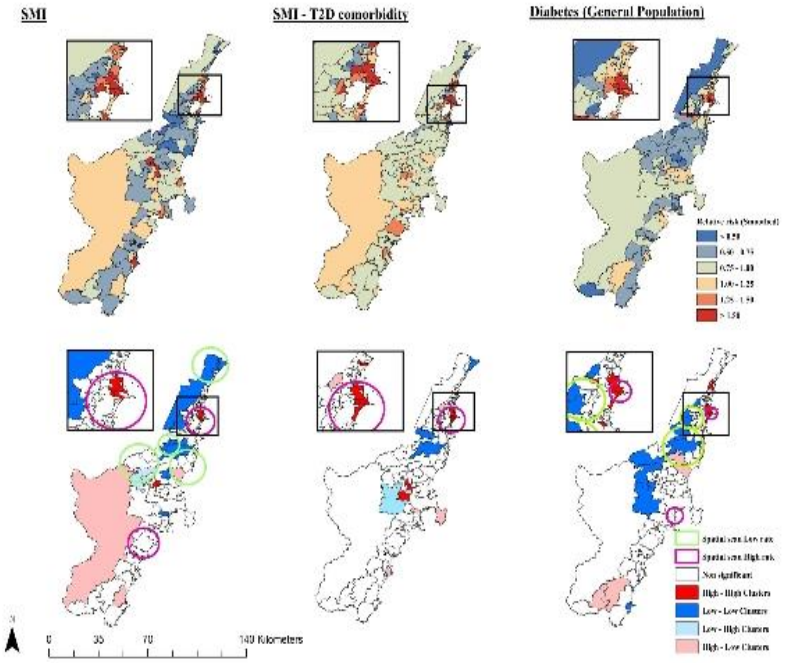

Fig 3. Geographic distribution and significant hotspots for SMI, diabetes and SMI -T2D comorbidity in Illawarra—Shoalhaven (2010–2017).

https://doi.org/10.1371/journal.pone.0225992.g003

Geographic concordance of SMI, T2D and their comorbidity

In order to compare the geographic concordance of SMI-T2D comorbidity with the SMI and diabetes risk in Illawarra Shoalhaven, smoothed relative risk maps, LISA maps and spatial scan statistics were generated for SMI, Gen-DM and SMI-T2D comorbidity (Fig 3). For SMI, we identified 6 high-high clusters, 10 low-low clusters, 4 low-high clusters and 8 high-low clusters. For Gen-DM the high-high, low-low, low-high and high-low clusters identified were 6, 12, 2 and 5 respectively. Both LISA and spatial scan statistics (Table 3) consistently identified a convergence of hotspots (high-high clusters) for SMI, T2D and their comorbidity in four urban suburbs south of the major metropolitan centre, which was previously identified as a comorbidity hotspot.

Fig 4 shows the result of bivariate LISA analysis and multivariate spatial scan for SMI and diabetes in Illawarra and Shoalhaven. Five high-high clusters indicating suburbs of higher SMI risk surrounded by neighbourhoods of higher diabetes risk were observed in the southern urban areas. The analysis also revealed 7 low-low clusters in the central part of study region. Similar to LISA clusters, application of multiple comparison correction to these results didn't yield any significant results. Multivariate spatial scan analysis with a maximum spatial cluster size of up to 50% identified one high rate cluster for both SMI and Gen-DM comprising of 4 suburbs with a relative risk of 1.63 (log likelihood ratio 178.8, $p < 0.001$).

Table 3. Significant spatial scan clusters of SMI, diabetes (general population) and SMI—T2D comorbidity (Illawarra -Shoalhaven 2010–2017).

Diagnosis	Cluster Type	No of suburbs	Observed count	Expected Count	Relative risk	Log likelihood	P value
SMI	High	24	1350	1056.13	1.43	53.54	<0.001
	High	12	222	152.37	1.49	14.58	<0.001
	Low	16	248	404.99	0.59	38.89	<0.001
	Low	3	1	26.21	0.038	22.02	<0.001
	Low	5	31	60.43	0.094	14.53	<0.001
SMI-T2D comorbidity	High	23	163	102.97	1.89	20.02	<0.001
Gen-DM	High	4	917	577.09	1.63	89.40	<0.001
	High	5	1157	967.84	1.21	18.86	<0.001
	Low	14	1076	1555.69	0.66	92.80	<0.001
	Low	12	570	732.79	0.77	20.65	<0.001

https://doi.org/10.1371/journal.pone.0225992.t003

Discussion

The present study identified geographic variations in the distribution of SMI–T2D comorbidity in the Illawarra Shoalhaven. The spatial dependence of comorbidity was confirmed by the global test for spatial autocorrelation (Moran's I). In other words, suburbs with higher comorbidity risk tend to locate closer than we would expect at random. Conversely, suburbs with lower comorbidity risk also tend to cluster together geographically. Using local indicators of spatial association (LISA and spatial scan statistics), we were able to identify a consistently higher burden of comorbidity in Six urban suburbs south of the metropolitan city. These suburbs are relatively homogeneous in terms of their population density and socioeconomic environments. Comparison of comorbidity hotspots with the hotspots of single diagnosis SMI and diabetes further revealed a geographic concordance of high-risk areas in four urban regions of the main metropolitan. These findings suggest that the population in some urban suburbs are challenged by SMI, T2D and their comorbidity and appropriate prevention and management initiatives should be targeted accordingly. This study has also demonstrated the potential usefulness of combining spatial analytical methods and clinical data information to inform health service commissioning and geographically target needs-based preventive interventions.

We observed that both LISA and bivariate LISA clusters became non-significant after correcting for multiple comparisons using Benjamini Hochberg procedure. Even though Benjamini–Hochberg correction is a less conservative method compared to other false discovery correction procedures, there can still be substantial loss of power (constraining the type I error rate at the expense of an increasing type II error rate) when dealing with bigger datasets [31]. This loss of power could have contributed to our null results. Despite this potential limitation, the correspondence between uncorrected LISA and spatial scan analyses in identifying hotspots south of the major metropolitan area indicate that our results remain interesting. This is the first study to explore the geographic variations in the distribution of SMI and T2D comorbidity. Lack of evidence in this important area of public health was highlighted in a recent systematic literature review[19]. Previous research has, however, established significant geographic inequalities and urban clustering in the distribution of both SMI and type 2 diabetes [13–18]. In this study, we were able to demonstrate that this relationship holds true for their comorbidity as well. From a health service research and policy perspective, describing the geography of coexisting diseases together might prove more useful in aiding decisions on the allocation of resources and integrated interventions. Findings from this study will also create opportunities for further exploratory hypothesis testing, using spatial clustering as a framework. One commonly hypothesised and plausible contributory exposure is neighbourhood

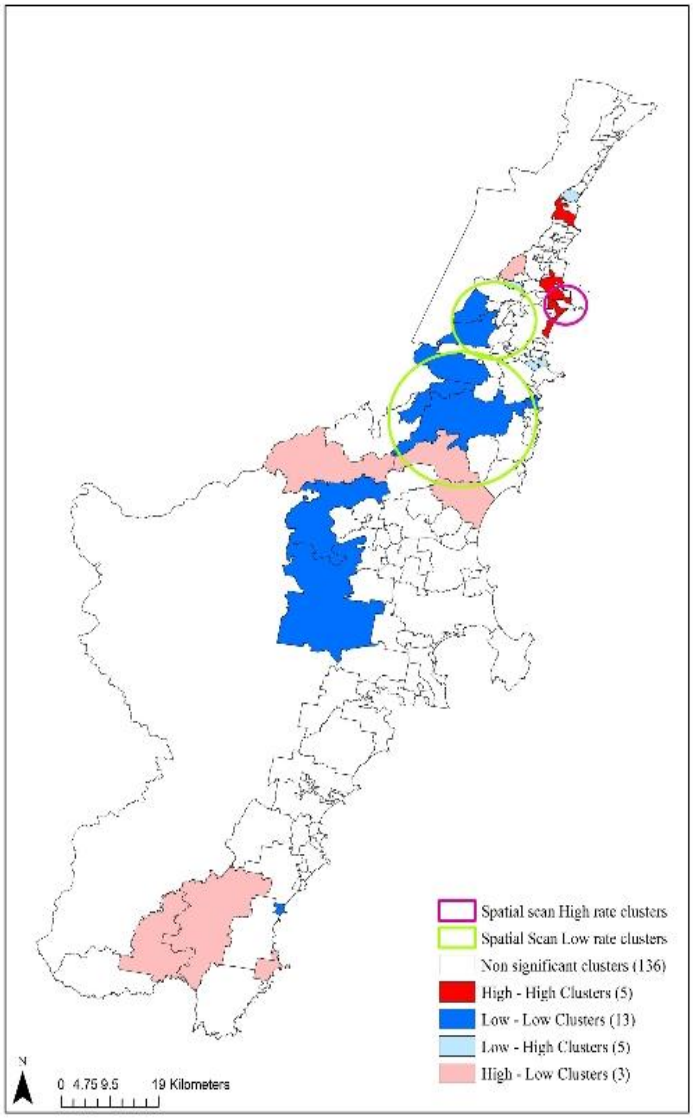

Fig 4. Bivariate LISA and multivariate spatial scan clusters showing the local association between SMI and diabetes in Illawarra and Shoalhaven (2010–2017).

https://doi.org/10.1371/journal.pone.0225992.g004

socioeconomic disadvantage. Disadvantaged neighbourhoods often expose mentally ill persons to greater psychosocial stress, or act as a proxy for adverse health behaviours such as unhealthy eating, lack of physical activity and obesity, which have been shown to be associated with increased T2D risk[17,34,35]. Thus, identification and exploration of these

neighbourhood features that might influence SMI -T2D comorbidity will be an important next step for enhancing our understanding of the geography of comorbidity and will be addressed in future research.

The overall aim of our study was to generate information that could be useful to guide health service policies and preventive interventions aimed at reducing the burden of T2D comorbidity in people with serious mental illness. We have identified hotspots of SMI, T2D and their comorbidity in some urban regions of the Illawarra–Shoalhaven. Targeted health care strategies focussed on these regions may possibly reduce the health inequality and public health burden imposed by SMI–T2D comorbidity.

The results from this study should be interpreted with respect to their limitations. Firstly, the serious mental illness and comorbidity data were sourced only from inpatient mental health records of ISLHD and did not consider outpatient and private practice records. Even though this is supported by the data from the Australian National Surveys of Psychosis (indicating that 45.6–62.9% of people with SMI reported $\geq$1 hospital admission for any reason in the previous 12 months)[36], the results from our study cannot be applied to the general population. The second limitation is the cross-sectional study design that does not permit cause and effect conclusions. We also note that there's a potential for temporal misalignment as 2011 census data was used as the reference population. However, a sensitivity analysis using 2016 census data did not alter the results significantly.

Conclusions

In this study we combined spatial analytical methods and clinical data to analyse the spatial distribution of SMI -T2D comorbidity in Illawarra Shoalhaven. Our results revealed evidence of spatial variations in the distribution of SMI -T2D comorbidity. The high-risk clusters were mainly located in the urban areas. The findings from this study emphasise the geographic focus needed in these regions to reduce the T2D burden in SMI. This study has also demonstrated the potential of spatial analytical methods in assessing and identifying spatial disparities in the comorbid disease risks so that preventive interventions and resources are appropriately targeted. Further investigation using multilevel analytical techniques is required to determine whether particular environmental factors such as neighbourhood socioeconomic disadvantage may be explanatory for these geographic variations in SMI -T2D comorbidity. Understanding the neighbourhood correlates will help us in developing evidence based holistic interventions, health care policies and potentially the design of healthier places to live.

Acknowledgments

We thank (i) Illawarra Health Information Platform (IHIP) research partnership established between the Illawarra Shoalhaven Local health District (ISLHD) and the University of Wollongong and (ii) Southern IML Research (SIMLR) study database for providing the data used in this study.

Author Contributions

Conceptualization: Ramya Walsan, Darren J. Mayne, Nagesh Pai, Xiaoqi Feng, Andrew Bonney.

Formal analysis: Ramya Walsan.

Investigation: Ramya Walsan.

Methodology: Ramya Walsan, Darren J. Mayne.

Project administration: Andrew Bonney.

Resources: Andrew Bonney.

Supervision: Darren J. Mayne, Nagesh Pai, Xiaoqi Feng, Andrew Bonney.

Validation: Andrew Bonney.

Visualization: Ramya Walsan.

Writing – original draft: Ramya Walsan.

Writing – review & editing: Ramya Walsan, Darren J. Mayne, Nagesh Pai, Xiaoqi Feng, Andrew Bonney.

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Appendix E: Published Study 2 article.

International Journal of
Environmental Research and Public Health

MDPI

Article

Examining the Association between Neighbourhood Socioeconomic Disadvantage and Type 2 Diabetes Comorbidity in Serious Mental Illness

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Received: 2 August 2019; Accepted: 12 October 2019; Published: 15 October 2019

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Abstract: This study examined the association between neighbourhood socioeconomic disadvantage and serious mental illness (SMI)–type 2 diabetes (T2D) comorbidity in an Australian population using routinely collected clinical data. We hypothesised that neighbourhood socioeconomic disadvantage is positively associated with T2D comorbidity in SMI. The analysis considered 3816 individuals with an SMI living in the Illawarra and Shoalhaven regions of NSW, Australia, between 2010 and 2017. Multilevel logistic regression models accounting for suburb (neighbourhood) level clustering were used to assess the association between neighbourhood disadvantage and SMI -T2D comorbidity. Models were adjusted for age, sex, and country of birth. Compared with the most advantaged neighbourhoods, residents in the most disadvantaged neighbourhoods had 3.2 times greater odds of having SMI–T2D comorbidity even after controlling for confounding factors (OR 3.20, 95% CI 1.42–7.20). The analysis also revealed significant geographic variation in the distribution of SMI -T2D comorbidity in our sample (Median Odds Ratio = 1.35) Neighbourhood socioeconomic disadvantage accounted for approximately 17.3% of this geographic variation. These findings indicate a potentially important role for geographically targeted initiatives designed to enhance prevention and management of SMI–T2D comorbidity in disadvantaged communities.

Keywords: neighbourhood disadvantage; serious mental illness; type 2 diabetes; comorbidity

1. Introduction

Serious mental illness (SMI) is a term used to refer to severe and persistent forms of mental disorders such as schizophrenia, bipolar disorder or major depression [1]. Individuals with SMI have 2 to 4 times increased risk of developing type 2 diabetes (T2D) compared with the general population which translates into a reduction of 15–20 years in their life expectancies [2–4]. A comorbid T2D diagnosis is also associated with other adverse consequences such as increased hospitalisations, greater

number of emergency department visits, non-adherence to treatments, higher healthcare utilisation costs, higher risk of cognitive deficit, poor clinical outcomes and decreased quality of life for the mentally ill. [2,5–11].

People with SMI are more likely to live in disadvantaged neighbourhoods [12,13] and the environment in these neighbourhoods may compound the experiences of psychosocial stress or promote engagement in adverse health behaviours (e.g. unhealthy eating and physical inactivity) and weight gain, all of which contribute to T2D risk [12,14,15]. A number of studies have found that the prevalence of SMI and T2D are both separately higher in more socioeconomically disadvantaged neighbourhoods [13,16–19]. However, research to date has not adequately examined the association between area-level disadvantage and SMI–T2D comorbidity. A recent systematic review [20] examining this relationship identified only a single study demonstrating a tentative association between the neighbourhood level disadvantage and T2D comorbidity in mental illness [21]. The aforementioned study, however, focused entirely on major depression and did not consider other forms of SMI such as schizophrenia or bipolar disorder. Hence additional research on the association between neighbourhood disadvantage and SMI–T2D comorbidity is warranted, given the paucity of evidence available and the plausibility of an association. We have recently reported significant geographic variations in the distribution of SMI–T2D comorbidity suggesting the need to explore the role of neighbourhood level disadvantage in explaining this variation [22].

Establishing strong evidence of the relationship between neighbourhood disadvantage and SMI –T2D comorbidity is an important step in advancing our understanding of the T2D comorbidity in SMI and the possible associations with neighbourhood environments might have with this comorbidity. Moreover, population-based prevention strategies that shift the risk distribution of entire population in a favourable direction are considered more effective and sustainable than the individual-based approaches in reducing the disease burden [23]. Understanding these associations may also be useful for health policymakers to develop integrated interventions and to provide greater diversity of care needed to optimally manage the complex needs associated with comorbidity.

The aim of this study was to investigate the association between neighbourhood socioeconomic disadvantage and SMI–T2D comorbidity in an Australian population using routinely collected clinical data. We hypothesised that greater socioeconomic disadvantage would be associated with increased T2D comorbidity in SMI. A further objective was to determine how much variance of SMI-T2D comorbidity between neighbourhoods was attributable to neighbourhood socioeconomic disadvantage.

2. Materials and Methods

2.1. Study Design and Sample

We used a cross-sectional, multilevel study design to examine the association between neighbourhood socioeconomic disadvantage and SMI-T2D comorbidity. The study area comprised the Illawarra and Shoalhaven regions of NSW, Australia, which had an estimated resident population of 368,604 people at the time of the 2011 Australian Census of Population and Housing [24]. The region has a mix of rural and urban influences and is comprised of the local government areas of Kiama, Shellharbour, Shoalhaven, and Wollongong. The socio-economic profile of the study area as described by region's socio-economic index scores are comparable to that of NSW and Australian average [25,26]. The data analysed in this study covered the period 01 January 2010 to 31 December 2017 and were retrieved from Illawarra Health Information Platform (IHIP). The IHIP is a research partnership established between Illawarra Shoalhaven Local Health District (ISLHD) and University of Wollongong for the purpose of providing ISLHD health service data to clinicians and researchers. The analysis was undertaken at the state suburb level (SSCs), which was the smallest geographic unit at which the health service data were available. State suburbs are the Australian Bureau of Statistics (ABS) approximation of suburbs gazetted by the Geographical Names Board of NSW [27]. The Illawarra-Shoalhaven region comprised of 167 suburbs with an average land area of 36.56 km^2 and 2207 residents each in 2011 [24].

This study was approved by the University of Wollongong and Illawarra Shoalhaven Local Health District Human Research Ethics Committee (protocol number 2017/428).

2.2. Measures

Data extraction was carried out using International Classification of Diseases (ICD) version 10 codes and was restricted to adults 18 years and over. We defined SMI as having a primary or secondary diagnosis of schizophrenia (F20), other non-affective psychosis (F22–F29), bipolar disorder (F30, F31), major depression (F32, F33) or other affective disorders (F34, F39) in the inpatient records of ISLHD. Diabetes comorbidity, the outcome of interest, was defined as having a T2D diagnosis (E11) in people with SMI and was extracted as either present or absent along with each of the SMI records. The analytical sample was formed by excluding individuals residing outside the Illawarra and Shoalhaven regions (n = 50) and individuals with no suburb (n = 283) or country of birth information (n = 8). The final SMI sample consisted of 3816 individuals of whom 463 (12.09 %) had T2D comorbidity.

Neighbourhood socioeconomic disadvantage was operationalised for suburbs using the Index of Relative socioeconomic disadvantage (IRSD) from the 2011 Socioeconomic Indexes for Area Census product [26]. An IRSD score reflects the aggregate level of socioeconomic disadvantage measured on the basis of 17 variables including education, income, occupation, unemployment, housing type, overcrowding, and English proficiency. For this study, IRSD scores for Illawarra and Shoalhaven suburbs were divided into quintiles of neighbourhood disadvantage with Quintile one (Q1) denoting the 20% most disadvantaged suburbs in Illawarra-Shoalhaven and Quintile five (Q5) the least disadvantaged 20%. Global Moran's I revealed a significant spatial dependence for neighbourhood socioeconomic disadvantage quintiles (Moran's I = 0.443673, $p < 0.0001$) indicating that suburbs with similar relative neighbourhood disadvantage are clustered geographically [28]. Quintiles were then assigned to individuals based on their suburb of residence at their most recent admission before 31 December 2017.

Individual-level variables included in the analysis were sex, age at most recent admission and the country of birth. Age was categorised into three age groups (18–44, 45–65, 65+) and sex were grouped as male or female. Country of birth data was aggregated based on the *Standard Australian Classification of Countries* produced by the Australian Bureau of Statistics [29].

2.3. Statistical Analysis

Multilevel logistic regression models accounting for suburb level clustering were used to assess the association between neighbourhood disadvantage and SMI–T2D comorbidity. The data structure consisted of two levels with individuals (level 1) nested within suburbs (level 2). A series of models were fit as follows: model 1 included only suburb level random effect, model 2 added individual level factors (age, gender, country of birth) to model 1, and model 3 added neighbourhood level IRSD quintiles to model 2. Interactions between individual variables and neighbourhood disadvantage were also considered in modelling to investigate any cross-level effect modification of the association by individual-level factors. Models were estimated using the maximum likelihood method with Laplace approximation [30]. Intra class correlation (ICC) and Median Odds ratios (MOR) were calculated for each model to assess how much of the variance in comorbidity could potentially be attributed to neighbourhoods [31,32]. ICC informs us regarding the variance between areas [31]. The MOR is interpreted as the increased risk in comorbidity when an individual moves to a suburb of higher disadvantage [33]. MOR closer to 1 implies little variation between areas whereas larger MOR values indicate considerable variation between areas [33]. We also reported proportional change in variance (PCV) to show how much of the residual variance was explained by the additional explanatory variables in each of the models. ICC, MOR, and PCV were derived from model outputs following the methods specified by Merlo et al and Austin et al [31,32]. Likelihood ratio tests were used to determine the goodness of fit of the models. All statistical analysis was completed using R version 3.5 [34]. Statistical significance in this analysis was set at $p < 0.05$.

3. Results

The descriptive characteristics of the study population are given in Table 1. SMI-T2D comorbidity was present in 13.3% of females and 11.1% of males with an SMI diagnosis. The age group with highest proportion of comorbidity was 65+ (27.73%). With regards to country of birth, a higher percentage of T2D comorbidity was observed for SMI individuals born in Middle East and North Africa (23.1%), Eastern and Central Europe (23.2%) and Western Europe (21.2%). The SMI-T2D comorbidity prevalence in the most disadvantaged IRSD quintile (Q1) was 13.1% (n = 229) and that in the least disadvantaged quintile (Q5) was 5.1% (n = 7).

Table 2 presents the results of the multilevel logistic regression analysis. Model 1 provides the estimate of between area variation in SMI–T2D comorbidity without any explanatory variables. The MOR for model 1 was 1.35, indicating some level of geographic variation in the distribution of SMI-T2D comorbidity in our sample. Moreover, the ICC for model 1 was 0.029, showing that 2.9% of the variance in comorbidity was attributable to between neighbourhood differences. The addition of individual level variables in model 2 accounted for 25.5% of between area variance and addition of IRSD in model 3 accounted for an additional 17.3% and reduced the MOR to 1.25. After inclusion of individual and neighbourhood variables, the ICC decreased from 2.9% to 1.7%.

Table 1. Characteristics of study population Variables.

Variables	Individuals with SMI n = 3816	Individuals with SMI–T2D Comorbidity n = 463	% of Individuals with SMI who Also Have Comorbidity (95% CI)
Individual variables			
Gender			
Female	1848 (48%)	245 (53%)	13.3 (11.8–14.9)
Male	1968 (52%)	218 (47%)	11.1 (9.7–12.5)
Age, years (Mean (SD))			
Age, years	43.6 (18.5)	58.8 (15.7)	
18–44	1961 (51%)	92 (20%)	4.7 (03.8–05.7)
45–65	1213 (32%)	193 (42%)	15.9 (13.9–18.0)
65+	642 (17%)	178 (38%)	27.7 (24.3–31.2)
Country of birth			
Australia	3104 (81%)	339 (73%)	10.9 (9.9–12.1)
Oceania excluding Australia	74 (2%)	12 (3%)	16.2 (9.5–26.2)
UK & Ireland	212 (6%)	35 (8%)	16.5 (12.1–22.1)
Western Europe	137 (4%)	29 (6%)	21.2 (15.2–28.8)
Eastern and Central Europe	125 (3%)	29 (6%)	23.2 (16.7–31.3)
North East Asia	17 (0%)	0 (0%)	0.0 (0–18.4)
South East Asia	51 (1%)	6 (1%)	11.8 (5.5–23.4)
Central and South Asia	16 (0%)	3 (1%)	18.8 (6.6–43.0)
Middle East and North Africa	39 (1%)	9 (2%)	23.1 (12.7–38.3)
Sub-Saharan Africa	20 (1%)	0 (0%)	0.0 (0–16.1)
Americas	21 (1%)	1 (0%)	4.8 (0.9–22.7)
Neighbourhood level variables			
IRSD as quintiles			
Q1 (Highest)	1752 (46 %)	229 (49%)	13.1 (11.6–14.7)
Q2	943 (25 %)	120 (26%)	12.7 (10.7–14.9)
Q3	620 (16 %)	75 (16%)	12.1 (9.8–14.9)
Q4	362 (10 %)	34 (7%)	9.4 (6.8–12.8)
Q5 (Lowest)	139 (4 %)	7 (2%)	5.1 (2.5–10.0)

IRSD = Index of Relative Socioeconomic Disadvantage.

Table 2. The association between neighbourhood socioeconomic disadvantage and serious mental illness (SMI)–type 2 diabetes (T2D) comorbidity using multilevel analysis (Illawarra – Shoalhaven, 2010–2017).

Variable	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Individual variables			
Gender		$p = 0.658$	$p = 0.687$
Female		1.00	1.00
Male		0.95 (0.78–1.17)	0.96 (0.78–1.17)
Age		$p < 0.05$	$p < 0.05$
18–44		1.00	
45–65		3.79 (2.91–4.93)	3.78 (2.90–4.92)
65+		7.68 (5.77–10.23)	7.82 (5.87–10.42)
Country of birth		$p = 0.137$	$p = 0.149$
Australia		1.00	1.00
Oceania excluding Australia		1.57 (0.81–3.03)	1.53 (0.79–2.97)
UK & Ireland		0.84 (0.57–1.26)	0.88 (0.59–1.31)
Western Europe		0.99 (0.63–1.54)	0.97 (0.62–1.52)
Eastern and Central Europe		1.30 (0.82–2.05)	1.30 (0.82–2.06)
South East Asia		1.30 (0.53–3.19)	1.30 (0.52–3.19)
Central and South Asia		2.03 (0.53–7.82)	2.13 (0.56–8.10)
Middle East and North Africa		1.84 (0.83–4.09)	1.87 (0.84–4.16)
Americas		0.42 (0.06–3.25)	0.41 (0.05–3.15)
Neighbourhood Variable			
IRSD quintiles			p <0.05
Q5 (Least disadvantaged)			1.00
Q4			1.87 (0.77–4.53)
Q3			2.67 (1.14–6.15)
Q2			2.92 (1.28–6.67)
Q1 (Most disadvantaged)			3.20 (1.42–7.20)
Variance of random effects			
T^2	0.098	0.073	0.056
PCV	Ref	25.5%	42.9%
ICC	0.029	0.0217	0.017
MOR	1.347	1.293	1.252

OR: Odds Ratio, 95% CI: 95% confidence interval, T^2: Area level variance, PCV: Proportional change in Variance, ICC: Intra Class Correlation, MOR: Median Odds Ratio, Model 1: Null model with suburb level random effect, Model2: Model 1 + individual-level factors, Model 3: Model 2+ neighbourhood level IRSD quintiles.

Results for individual-level variables in Model 2 indicate that age was significantly associated with SMI-T2D comorbidity. Older individuals with SMI have significantly higher odds of having T2D comorbidity compared with younger individuals. Model 3 showed a significant association between higher levels of neighbourhood disadvantage and diabetes comorbidity in SMI after controlling for age, gender and country of birth. Living in a neighbourhood with the highest socioeconomic disadvantage was associated with 3 times increased odds of having SMI-T2D comorbidity compared with the least disadvantage neighbourhood (OR 3.20, 95% CI 1.42–7.20 for Q1 vs Q5). Including two-way interaction terms in Model 3 indicated no evidence of effect modification of the association between SMI–T2D comorbidity and IRSD by age ($\chi^2_{LRT} = 14.16$, DF = 8, $p = 0.077$), gender ($\chi^2_{LRT} = 1.45$, DF = 4, $p = 0.835$) or country of birth ($\chi^2_{LRT} = 30.68$, DF = 38, $p = 0.794$).

4. Discussion

We found an independent positive association between neighbourhood disadvantage and SMI–T2D comorbidity after controlling for individual age, gender and country of birth. Neighbourhood socioeconomic disadvantage accounted for 17.3% of the between neighbourhood variation in SMI–T2D comorbidity. Among the individual-level factors, age was independently associated with SMI–T2D comorbidity. Individual factors accounted for 25.5% of the between neighbourhood variation. Neither gender nor country of birth were associated with SMI-T2D comorbidity. Lower neighbourhood variance in SMI–T2D comorbidity (ICC = 0.029) reported in our study does not preclude important neighbourhood level effects [35]. Misspecification of neighbourhoods, smaller group sizes and even omission of a relevant level 1 variable can all cause under estimation of neighbourhood variance [36]. Low Intra class correlation (ICC) can coexist with important neighbourhood level fixed effects and several of these examples are available in public health where risk factors explain very little neighbourhood variance but are important predictors of health outcomes [36]. Additionally, Geoffrey Rose had pointed out that even small neighbourhood effects, when aggregated at population scales, can have a massive impact [23]. Ours appears to be one of the first studies to explore the association between area level disadvantage and SMI–T2D comorbidity. The only other study addressing this research question investigated major depression only and reported a positive but non-significant association between area level disadvantage and SMI–T2D comorbidity [21]. Our findings are, however, consistent with prior studies, which show significant neighbourhood level socioeconomic inequalities in the distribution of SMI [13,17,37] and T2D [18,19,38,39] as independent conditions. In their systematic review, Mair et al identified 45 studies, of which 37 reported significant associations between neighbourhood characteristics and depression [40]. Similarly, the significant associations between neighbourhood environments and T2D risk were revealed in another systematic review by Dendup et al. [41]. The findings of a positive significant association between SMI–T2D comorbidity and age and a non-significant association between SMI–T2D comorbidity and gender are consistent with previous reports in the literature [3,42,43].

The results of this study have policy implications for planning interventions and resourcing public health services. Our results indicate that efforts to reduce diabetic comorbidity in serious mental illness might benefit by focussing on individuals with SMI living in high deprivation neighbourhoods. These results also have future research implications. Understanding why neighbourhood level disadvantage is associated with comorbidity is an important next step in addressing these inequities and in developing sustainable interventions and long-term solutions. There are several plausible explanations for increased SMI–T2D comorbidity in more disadvantaged neighbourhoods, over and above individual level factors. Neighbourhood level features, such as green spaces, access to health care services, availability of fast food restaurants and area level crime may be differentially present in advantaged and disadvantaged neighbourhoods [44]. These may in turn act as a stimulus for chronic stress or adverse health behaviours such as unhealthy eating, lack of physical activity and obesity, which have been shown to be associated with increased T2D risk [12,14,15]. Further exploration of the mediating or confounding roles played by these contextual variables may improve our understanding of SMI–T2D comorbidity and the casual pathways linking them with the neighbourhood environments.

There are some limitations to our study. First, the cross-sectional study design does not allow us to draw cause-effect conclusions. Second, we used data sourced only from inpatient mental health records and did not consider outpatient and private practice records. However, the Australian National Surveys of Psychosis indicates that 45.6–62.9% of people with SMI reported ≥1 hospital admission for any reason in the previous 12 months [45], which should have provided a reasonable coverage given our eight-year data collection period. In addition, we acknowledge the potential for temporal misalignment as 2011 relative disadvantage index scores were used in this analysis. Nonetheless a weighted Kappa analysis between 2011 and 2016 disadvantage quintiles revealed a good agreement between the two (k = 0.796) indicating that the deprivation scores have remained relatively similar during these periods. Individual socioeconomic status, ethnicity, age at diagnosis and number of

hospital admissions, were not included in this analysis due to the lack of data availability. This may have resulted in the overestimation of neighbourhood level effects. Finally, we also acknowledge the potential for reverse causation as SMI and T2D share a bidirectional association.

5. Conclusions

Our results indicate that the people with SMI living in the most disadvantaged neighbourhoods are more likely than their counterparts in the least disadvantaged neighbourhoods to report SMI-T2D comorbidity. These findings highlight the need to consider public health prevention strategies at both individual and neighbourhood level in order to reduce the public health burden imposed by comorbidity. The current study makes a significant contribution to the scant research literature available in this area of public health. Future research is needed to extend these findings and to consider how various neighbourhood contextual features may mediate the effect of neighbourhood socioeconomic disadvantage on SMI–T2D comorbidity.

Author Contributions: R.W. conceived the idea for the study, undertook literature review, analyzed data, wrote the first draft and completed the manuscript. A.B., D.J.M, N.P., and X.F. supervised the project, contributed to the study design, data analysis and drafting of the manuscript. R.W., A.B., D.J.M., N.P., and X.F. all critically reviewed the manuscript and helped draft the final version for submission.

Funding: This research was conducted with the support of the Australian Government Research Training program scholarship and Illawarra Shoalhaven local health district – University of Wollongong combined scholarship.

Acknowledgments: We thank the Illawarra Health Information Platform (IHIP) research partnership established between the Illawarra Shoalhaven Local health District (ISLHD) and the University of Wollongong for providing the data used in this study.

Conflicts of Interest: The authors declare no conflict of interest.

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Appendix F: Sensitivity analysis excluding neighbourhood level obesity

Variables	Odds ratio (95 % Cl) (Model 4)*	P value
Sex		
Female	1.00	
Male	0.96 (0.78–1.18)	0.685
Age		
18 - 44	1.00	
45–65	3.77 (2.89 – 4.92)	
65+	7.84 (5.87 –10.46)	
		<0.001
Country of birth		
Australia	1.00	
Oceania excluding Australia	1.55 (0.80 – 3.00)	
UK & Ireland	0.84 (0.57 - 1.26)	
Western Europe	0.96 (0.61 -1.54)	
Eastern and central Europe	1.33 (0.84 – 2.01)	
South East Asia	1.20 (0.49 – 2.95)	
Central and South Asia	2.08 (0.55–7.92)	
Middle East and North Africa	1.85 (0.83–4.14)	
Americas	0.39 (0.05–3.04)	0.145
IRSD quintiles		
Q5 (Least disadvantaged)	1.00	
Q4	1.66 (0.62 -4.47)	
Q3	1.59 (0.60–4.26)	
Q2	1.88 (0.70–5.04)	
Q1(Most disadvantaged)	1.79 (0.66–4.83)	0.753
Area level crime		
Q5 (Lowest crime)	1.00	
Q4	0.95 (0.35 -2.68)	
Q3	1.49 (0.54–4.09)	
Q2	2.16 (0.79–5.89)	
Q1(Highest crime)	2.78 (1.02–7.58)	<0.001
Health care access		
Q5 (Lowest access)	1.00	
Q4	1.12 (0.50–2.49)	
Q3	1.00 (0.45–2.22)	
Q2	0.86 (0.37–1.94)	
Q1(Highest access)	1.34 (0.57–2.95)	0.354
Green spaces		
Q5 (Lowest available)	1.00	
Q4	0.90 (0.65–1.25)	
Q3	1.02 (0.70–1.49)	
Q2	1.08 (0.69–1.71)	
Q1(Highest available)	1.06 (0.49–2.32)	0.945
Fast food availability		
Available	1.00	
Not available	1.46 (1.04–2.03)	0.065

*Full model excluding neighbourhood level obesity

Appendix G: Neighbourhood and Individual interactions (Study 3)

Likelihood ratios for the two-way interactions' effects (individual and neighbourhood interactions)

Interaction terms	χ^2 LRT	Degrees of freedom	P value
Area level crime X age	10.50	8	0.231
Area level crime X sex	4.21	4	0.379
Area level crime X COB	6.44	35	1.000
Health care access X age	4.45	8	0.814
Health care access X sex	3.83	4	0.429
Health care access X COB	16.72	30	0.976
Green space X age	2.92	8	0.939
Green space X sex	1.57	4	0.815
Green space X COB	22.47	36	0.961
Neighbourhood obesity X age	11.28	8	0.186
Neighbourhood obesity X sex	4.96	4	0.291
Neighbourhood obesity X COB	5.55	36	1.000
Fast food availability X age	0.03	3	0.982
Fast food availability X sex	4.70	1	0.053
Fast food availability X COB	15.63	10	0.110

LRT – Likelihood ratio test, COB – Country of birth

Neighbourhood variables and age interactions

Neighbourhood variables	Age					
	45 -65			65+		
	Coefficient (β)	Standard error	P value	Coefficient (β)	Standard error	P value
Area level crime						
Q1	-14.39	6.64	0.070	-12.59	6.66	0.059
Q2	-14.32	6.64	0.061	-12.95	6.66	0.058

Q3	-14.35	6.65	0.070	-12.48	6.67	0.061
Q4	-13.60	6.67	0.061	-12.40	6.69	0.063
Health care access						
Q1	-0.08	1.30	0.953	-1.34	1.18	0.257
Q2	0.06	1.30	0.963	-1.34	1.19	0.259
Q3	0.28	1.29	0.826	-0.99	1.17	0.395
Q4	0.24	1.31	0.850	-0.92	1.20	0.440
Green space						
Q1	-0.45	0.83	0.591	-0.98	0.90	0.276
Q2	0.59	0.56	0.296	0.44	0.57	0.444
Q3	0.15	0.37	0.691	0.59	0.56	0.296
Q4	0.27	0.37	0.469	0.07	0.39	0.866
Neighbourhood obesity						
Q1	-0.33	1.29	0.800	-0.98	1.25	0.432
Q2	0.17	1.30	0.897	-0.46	1.26	0.713
Q3	-0.32	1.31	0.804	-0.22	1.27	0.858
Q4	-0.07	1.32	0.958	-1.02	1.29	0.426
Fast food availability						
Not available	-0.05	0.34	0.873	-0.06	0.37	0.861

Neighbourhood variables and sex interactions

Neighbourhood variables	**Sex**		
	Male		
	Coefficient (β)	**Standard error**	**P value**
Area level crime			
Q1	-0.68	0.92	0.458
Q2	-0.79	0.93	0.392

Q3	-0.71	0.95	0.450
Q4	-1.67	1.04	0.108
Health care access			
Q1	-0.87	0.80	0.277
Q2	-0.70	0.80	0.387
Q3	-0.91	0.79	0.249
Q4	-0.43	0.81	0.599
Green space			
Q1	0.34	0.72	0.636
Q2	-0.14	0.39	0.725
Q3	-0.02	0.29	0.958
Q4	0.289	0.28	0.309
Neighbourhood obesity			
Q1	-0.37	0.95	0.694
Q2	-0.01	0.96	0.990
Q3	-0.57	0.96	0.553
Q4	0.04	0.98	0.965
Fast food availability			
Not available	0.60	0.27	0.050

Neighbourhood variables and country of birth interactions

Neighbourhood variables	**Country of birth**				
	Oceania	**UK & Ireland**	**Western Europe**	**Eastern & Central Europe**	**South East Asia**

	Coefficient (β)	Standard error	P value	Coefficient (β)	Standard error	P value	Coefficient (β)	Standard error	P value	Coefficient (β)	Standard error	P value	Coefficient (β)	Standard error	P value
Area level crime															
Q1	0.82	1.55	0.596	-0.80	1.26	0.523	15.29	3.71	0.996	15.97	4.63	0.997	13.30	4.65	0.998
Q2	0.33	0.83	0.689	-0.97	1.30	0.459	14.82	3.72	0.997	15.66	4.62	0.997	14.41	4.66	0.998
Q3	0.42	0.94	0.653	-1.19	1.38	0.387	15.78	3.71	0.997	15.91	4.62	0.997	14.95	4.65	0.997
Q4	-15.01	3.11	0.996	-0.35	1.41	0.807	16.21	3.71	0.997	0.63	4.93	0.999	-0.31	8.08	1.00
Health care access															
Q1	16.24	3.72	0.997	-2.11	1.56	0.177	16.38	3.68	0.996	14.32	6.58	0.998	1.83	1.39	0.187
Q2	16.18	3.71	0.997	-1.20	1.55	0.438	15.99	3.67	0.997	15.25	6.59	0.998	0.66	1.42	0.643
Q3	14.93	3.71	0.997	-1.70	1.53	0.267	15.69	3.67	0.997	14.37	6.58	0.998	-0.92	1.36	0.494
Q4	14.65	3.72	0.997	-1.87	1.55	0.228	16.04	3.67	0.997	14.84	6.58	0.998	-0.08	1.64	0.962
Green space															
Q1	-15.22	6.59	0.998	-16.37	2.10	0.993	-16.05	3.69	0.997	-17.21	3.74	0.996	-16.24	6.58	0.998
Q2	3.25	1.09	0.060	0.93	0.61	0.129	1.32	0.82	0.108	-0.16	1.19	0.893	2.70	1.64	0.100
Q3	2.68	1.02	0.059	-0.30	0.63	0.629	0.66	0.60	0.275	-0.91	0.83	0.274	-15.04	1.93	0.994
Q4	1.32	1.01	0.190	-0.47	0.54	0.389	0.31	0.58	0.599	-0.55	0.65	0.400	1.60	1.27	0.209
Neighbourhood obesity															
Q1	1.30	0.92	0.945	0.37	1.24	0.976	16.15	6.57	0.998	16.58	6.56	0.998	15.65	4.62	0.997
Q2	1.13	0.85	0.181	0.11	1.25	0.931	16.17	6.57	0.998	16.73	6.56	0.998	14.80	4.62	0.997
Q3	0.86	0.93	0.353	-0.29	1.27	0.819	16.71	6.57	0.998	16.53	6.56	0.998	-0.95	4.79	1.00
Q4	0.26	1.28	0.839	0.37	1.26	0.769	16.41	6.57	0.998	15.95	6.56	0.998	-0.49	5.95	1.00
Fast food availability															
Not available	1.83	0.79	0.052	-1.26	0.59	0.053	0.39	0.54	0.473	-1.94	1.09	0.077	-15.54	2.17	0.994

Only the major country of birth groups reported

Likelihood ratio's for the two-way interactions effects (neighbourhood variables interactions)

Interaction terms	**χ^2 LRT**	**Degrees of freedom**	**P value**
Area level crime X irsd	7.94	14	0.892
Area level crime X Health care access	9.00	16	0.913
Area level crime X Green space	11.19	16	0.798
Area level crime X Neighbourhood obesity	8.27	15	0.912
Area level crime X Fast food availability	11.14	4	0.052
Health care access X irsd	2.81	15	0.997
Health care access X Green space	12.06	15	0.674
Health care access X Neighbourhood obesity	13.07	15	0.597
Health care access X fast food availability	0.44	4	0.979
Green space X irsd	18.22	16	0.311
Green space X Neighbourhood obesity	20.46	16	0.200
Green space X Fast food availability	6.61	4	0.157
Neighbourhood obesity X irsd	4.74	15	0.994
Neighbourhood obesity X fast food availability	7.51	8	0.111
Fast food availability X irsd	4.03	4	0.402

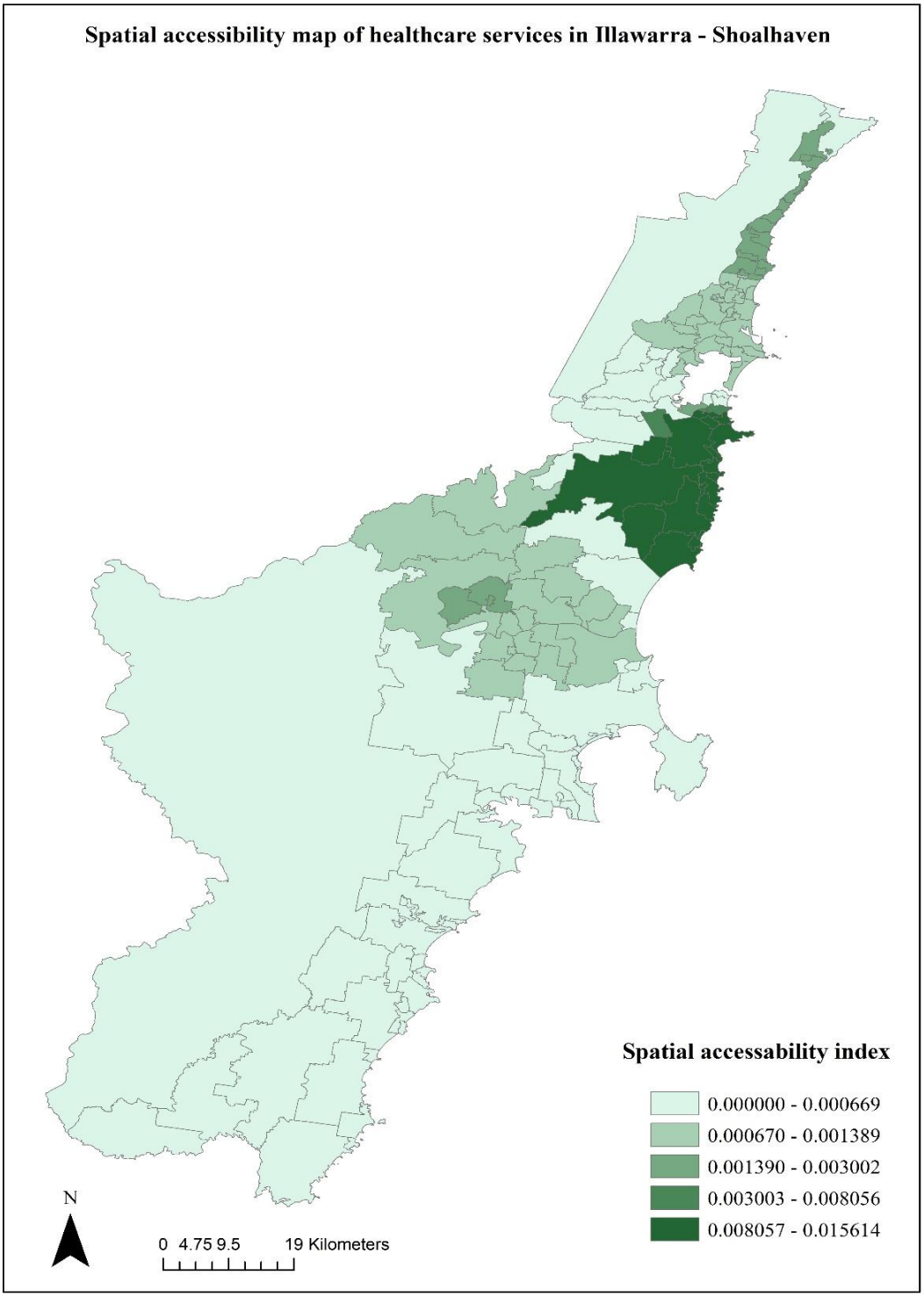
LRT – Likelihood ratio test, irsd – Index of relative socio-economic disadvantage

Interactions between neighbourhood variables

Neighbourhood variables	Neighbourhood socioeconomic disadvantage											
	Q1			Q2			Q3			Q4		
	Coefficient (β)	Standard error	P value	Coefficient (β)	Standard error	P value	Coefficient (β)	Standard error	P value	Coefficient (β)	Standard error	P value
Area level crime												
Q1	8.92	4.56	0.995	-15.23	7.64	0.998	13.43	5.65	0.997	-14.76	7.64	0.999
Q2	12.73	7.65	0.998	-2.68	1.48	0.070	12.76	7.65	0.999	-2.29	1.48	0.122
Q3	28.81	8.21	0.997	14.87	3.01	0.996	30.41	8.21	0.997	14.79	3.01	0.996
Q4	14.98	7.64	0.998	-0.46	1.29	0.725	-0.74	8.02	0.999	-0.49	1.34	0.712
Health care access												
Q1	-14.43	3.05	0.996	1.05	4.13	1.000	-13.85	3.05	0.996	-0.51	1.43	0.786
Q2	-15.00	3.05	0.996	0.28	4.13	1.000	-14.24	3.05	0.996	-0.46	1.10	0.675
Q3	-15.06	5.46	1.000	0.62	4.13	1.000	-14.76	3.05	0.996	-0.79	1.16	0.498
Q4	-0.51	5.46	1.000	15.13	6.13	0.998	0.41	5.46	1.000	13.99	4.53	0.998
Green space												
Q1	1.45	1.67	0.382	3.21	1.74	0.066	0.71	1.68	0.673	2.13	1.90	0.261
Q2	2.90	1.56	0.066	2.09	1.56	0.185	1.43	1.59	0.370	1.74	1.66	0.294
Q3	3.51	1.68	0.039	2.83	1.76	0.108	2.68	1.73	0.121	2.55	1.73	0.140
Q4	16.13	1.87	0.993	16.34	1.88	0.993	15.78	1.87	0.993	15.48	1.87	0.993
Neighbourhood obesity												
Q1	-2.13	2.20	0.991	-4.69	1.34	0.726	1.66	4.70	0.997	-1.61	7.39	0.998
Q2	-1.50	2.35	0.995	-1.62	2.35	0.995	1.39	5.25	1.000	-1.53	2.35	0.995
Q3	-3.09	4.28	0.994	-1.46	2.34	0.995	2.47	5.25	1.000	-1.44	2.35	0.995
Q4	-1.56	2.32	0.995	-1.64	2.35	0.994	7.60	5.25	1.000	-1.63	2.35	0.994
Fast food availability												
Not available	-0.50	1.15	0.664	-1.17	1.20	0.335	-0.63	1.17	0.587	-1.35	1.23	0.274
Area level crime												
	Q1			**Q2**			**Q3**			**Q4**		
Health care access												
Q1	17.01	7.46	0.998	-0.18	4.73	1.000	0.16	4.73	1.000	15.74	5.53	0.998
Q2	16.41	6.95	0.998	-1.97	3.89	1.000	-0.29	3.90	1.000	15.50	4.82	0.997
Q3	0.29	6.67	1.000	-16.51	3.34	0.996	-16.49	3.35	0.996	-1.16	4.39	1.000
Q4	0.59	6.66	1.000	-16.93	3.35	0.996	-16.84	3.35	0.996	-16.58	5.05	0.997
Greenspace												
Q1	1.16	1.46	0.427	0.16	1.24	0.900	-0.92	1.59	0.562	-16.72	2.20	0.994

Q2	16.44	3.37	0.996	16.83	3.37	0.996	15.56	3.37	0.996	15.41	3.37	0.996
Q3	0.88	1.12	0.428	0.94	1.12	0.400	0.08	1.15	0.945	-0.12	1.28	0.921
Q4	15.52	3.85	0.997	16.04	3.85	0.997	15.45	3.85	0.997	-0.54	4.19	1.000
Neighbourhood Obesity												
Q1	0.36	5.34	1.000	-15.43	4.67	0.997	0.45	5.34	1.000	-0.68	5.34	1.000
Q2	-15.36	2.81	0.996	-15.79	4.53	0.996	-15.29	2.81	0.996	-18.42	2.82	0.995
Q3	-15.49	2.82	0.996	-15.71	4.53	0.997	-15.45	2.81	0.995	-17.98	2.81	0.995
Q4	-15.23	2.81	0.996	-15.18	4.53	0.997	-14.98	2.81	0.996	-16.77	2.81	0.995
Fast food availability												
Not available	-0.01	0.95	0.986	0.211	0.94	0.824	-1.36	1.07	0.203	-1.12	1.03	0.280
Health care access												
	Q1			**Q2**			**Q3**			**Q4**		
Green space												
Q1	1.34	0.87	0.458	15.95	2.20	0.994	0.98	1.73	0.570	0.65	1.75	0.709
Q2	-14.65	4.34	0.997	16.55	2.20	0.994	-0.13	1.81	0.942	1.22	1.70	0.472
Q3	0.65	1.33	0.625	16.45	2.20	0.994	0.86	1.76	0.624	1.62	1.68	0.336
Q4	1.49	1.19	0.211	17.25	2.20	0.994	0.88	1.81	0.626	1.47	1.71	0.390
Neighbourhood obesity												
Q1	-1.12	4.97	1.000	-3.94	4.97	1.000	-1.53	1.21	0.986	-5.06	4.98	1.000
Q2	-1.72	3.42	0.996	-1.79	3.42	0.996	-1.79	3.61	0.996	-1.71	3.42	0.996
Q3	-1.62	3.42	0.996	-1.72	3.42	0.996	-1.63	3.61	0.996	-1.61	3.42	0.996
Q4	-3.32	8.20	1.000	-3.29	8.20	1.000	-6.77	8.28	1.000	-2.34	8.25	1.000
Fast food availability												
Not available	0.36	0.85	0.675	0.43	0.89	0.625	0.37	0.83	0.657	0.52	0.86	0.543
Green space												
	Q1			**Q2**			**Q3**			**Q4**		
Neighbourhood obesity												
Q1	-1.48	5.81	1.000	-2.65	5.86	1.000	-2.35	5.86	1.000	-0.30	5.86	1.000
Q2	-14.81	3.54	0.997	-16.63	3.58	0.996	-15.61	3.58	0.997	-15.51	3.58	0.997
Q3	-15.69	3.56	0.997	-16.59	3.85	0.996	-16.45	3.56	0.996	-15.72	3.58	0.997
Q4	-15.73	3.58	0.997	-16.05	3.58	0.996	-16.41	3.58	0.996	-14.98	3.59	0.997
Fast food availability												
Not available	-1.82	0.79	0.051	-0.58	0.48	0.227	-0.44	0.41	0.915	-0.40	0.45	0.369
Neighbourhood obesity												
	Q1			**Q2**			**Q3**			**Q4**		
Fast food availability												
Not available	0.35	0.93	0.712	-0.82	0.95	0.392	0.09	0.95	0.921	0.10	0.95	0.915

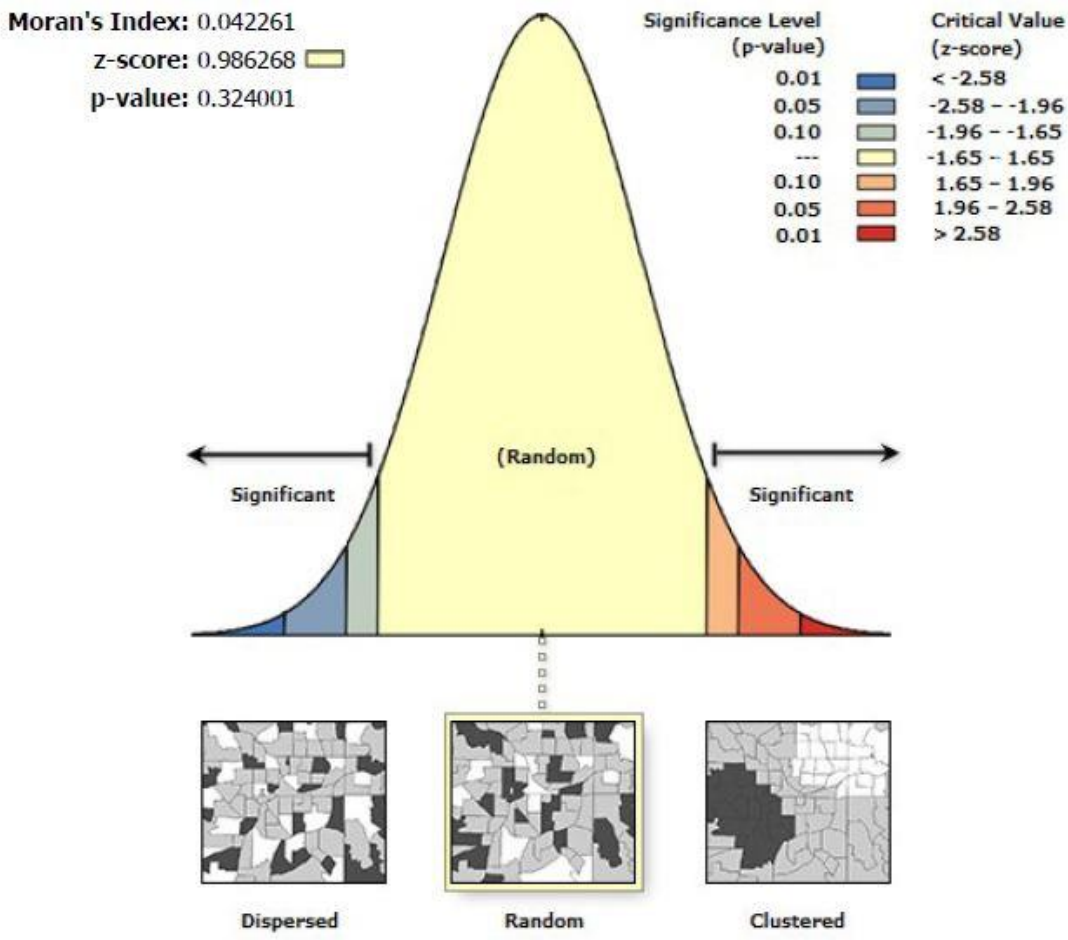
Appendix H: Spatial accessibility of health care access in Illawarra Shoalhaven (2010 – 2017).



Appendix I: Spatial autocorrelation of residuals

Moran's I - Study 2 residuals

Spatial Autocorrelation Report



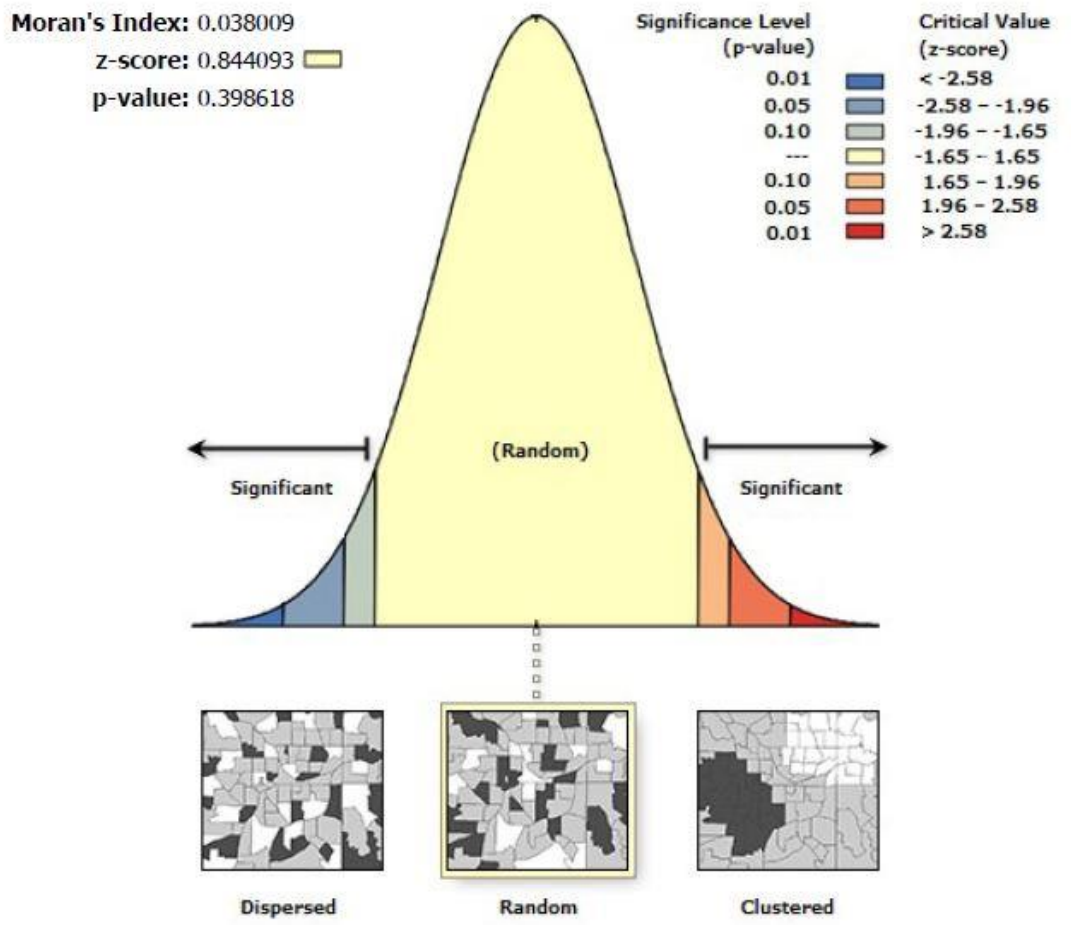
Given the z-score of 0.98626827068, the pattern does not appear to be significantly different than random.

Global Moran's I Summary

Moran's Index:	0.042261
Expected Index:	-0.006173
Variance:	0.002412
z-score:	0.986268
p-value:	0.324001

Moran's I - Study 3 residuals

Spatial Autocorrelation Report



Given the z-score of 0.844092534303, the pattern does not appear to be significantly different than random.

Global Moran's I Summary

Moran's Index:	0.038009
Expected Index:	-0.006173
Variance:	0.002740
z-score:	0.844093
p-value:	0.398618

Appendix J: Calculation of population averaged odds ratios

Population average coefficients are approximated from cluster specific regression coefficient based on the following formula [1]

$$\alpha_{PA} = \frac{\alpha_{CS}}{\sqrt{1 + (16^2 \times \frac{3}{(15 \times \pi)^2}) \times \tau^2}}$$

Where, α_{cs} is the conditional regression coefficient and T^2 is the variance of the random effects.

References

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1. Austin, P.C. and J. Merlo, *Intermediate and advanced topics in multilevel logistic regression analysis.* Statistics in Medicine, 2017. **36**(20): p. 3257-3277.

Appendix K: Multilevel regression analysis using neighbourhood variables as quartiles

Variables	**Model 4***	
	Odds ratio	**P value**
Sex		
Female	1.00	
Male	0.95 (0.77 - 1.16)	0.673
Age		
18 - 44	1.00	
45–65	3.77 (2.88 - 4.92)	
65+	7.78 (5.83 - 10.38)	<0.001
Country of birth		
Australia	1.00	
Oceania excluding Australia	1.64 (0.85 - 3.18)	
UK & Ireland	0.86 (0.58 - 1.29)	
Western Europe	0.96 (0.61 -1.50)	
Eastern and central Europe	1.32 (0.83 - 2.09)	
South East Asia	1.18 (0.48 – 2.91)	
Central and South Asia	2.10 (0.56 - 7.96)	
Middle East and North Africa	1.86 (0.84 - 4.15)	
Americas	0.45 (0.06 - 3.50)	0.164
IRSD quintiles		
Q5 (Least disadvantaged)	1.00	
Q4	1.88 (0.75 - 4.69)	
Q3	2.21 (0.90 – 5.42)	
Q2	2.33 (0.93 - 5.82)	
Q1(Most disadvantaged)	2.48 (0.95 – 6.47)	0.062
Area level crime		
Q4 (Lowest crime)	1.00	
Q3	1.73 (1.18 – 2.52)	0.003
Q2	2.32 (1.58 – 3.41)	
Q1(Highest crime)	2.54 (1.69 – 3.87)	
Health care access		

Q4 (Lowest access)	1.00	
Q3	1.04 (0.73 – 1.47)	
Q2	1.03 (0.72 – 1.47)	
Q1(Highest access)	1.17 (0.81 – 1.70)	0.672
Neighbourhood Obesity		
Q4 (Lowest Obesity)	1.00	
Q3	0.84 (0.54 – 1.31)	
Q2	0.87 (0.60 – 1.25)	
Q1(Highest Obesity)	0.87 (0.57 – 1.32)	0.143
Green spaces		
Q5 (Lowest available)	1.00	
Q4	0.94 (0.40 – 2.23)	
Q3	1.05 (0.45 – 2.44)	
Q2	0.79 (0.34 - 1.83)	0.615
Q1(Highest available)	0.87 (0.38 - 2.01)	
Fast food availability		
0	1.00	
1 -2	0.72 (0.55 – 1.04)	0.059
3 and above	0.73 (0.56 – 1.05)	

Appendix L : Published study 3 article

Original Research

Journal of Primary Care & Community Health
Volume 11: 1–11

DOI: 10.1177/2150132720924989
journals.sagepub.com/home/jpc
SAGE

Neighborhood Environment and Type 2 Diabetes Comorbidity in Serious Mental Illness

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Abstract

Aim: The aim of this study was to examine the association between neighborhood characteristics and type 2 diabetes (T2D) comorbidity in serious mental illness (SMI). We investigated associations of neighborhood-level crime, accessibility to health care services, availability of green spaces, neighborhood obesity, and fast food availability with SMI-T2D comorbidity. **Method:** A series of multilevel logistic regression models accounting for neighborhood-level clustering were used to examine the associations between 5 neighborhood variables and SMI-T2D comorbidity, sequentially adjusting for individual-level variables and neighborhood-level socioeconomic disadvantage. **Results:** Individuals with SMI residing in areas with higher crime rates per 1000 population had 2.5 times increased odds of reporting T2D comorbidity compared to the individuals with SMI residing in lower crime rate areas after controlling for individual and areal level factors (95% CI 0.91-6.74). There was no evidence of association between SMI-T2D comorbidity and other neighborhood variables investigated. **Conclusion:** Public health strategies to reduce SMI-T2D comorbidity might benefit by targeting on individuals with SMI living in high-crime neighborhoods. Future research incorporating longitudinal designs and/or mediation analysis are warranted to fully elucidate the mechanisms of association between neighborhoods and SMI-T2D comorbidity.

Keywords

serious mental illness, type 2 diabetes, neighborhood characteristics

Date received: 21 February 2020; accepted: 16 April 2020

Introduction

Research literature reports a type 2 diabetes (T2D) prevalence rate of approximately 13% in populations with serious mental illnesses (SMI) such as schizophrenia, bipolar disorder, or major depression.[1] This represents a 2 to 4 fold increase in risk compared with the general population.[1,2] Both SMI and T2D contribute significant individual and public health burdens when present independently, and are the 2 leading causes of morbidity worldwide.[3] The comorbidity compounds this burden by worsening the outcomes for each condition.[4] Type 2 diabetes comorbidity in SMI is associated with several adverse consequences such as increased mortality; reduced life expectancy of up to 30 years; worse cognitive decline; poor clinical and functional outcomes; higher health care costs; and reduced quality of life for people with mental illness.[2,5,6]

Neighborhood characteristics have been extensively linked to traditional risk factors of T2D such as physical inactivity, poor-quality diet, stress, and obesity.[7-11] Some studies have also investigated more specific features of neighborhood environments in relation to T2D risk. For example, reports from the Multiethnic Study of Atherosclerosis indicated that living in a neighborhood with better resources for physical activity and healthy food was associated with

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lower prevalence of insulin resistance[12] and lower incidence of T2D.[10,13] Sundquist et al[14] reported negative associations between neighborhood built environmental features and T2D risk in a large sample of Swedish adults. Studies from Australia have reported significantly lower incidence of T2D in greener neighborhoods after controlling for sociodemographic factors.[15,16] Neighborhood social features such as safety and crime were also found to be associated with conditions related to diabetes such as obesity, reduced physical activity, and psychological distress.[17-19] Neighborhood characteristics have also been associated with SMI.[20-24] Neighborhood-level research on SMI has investigated a wide range of features, including accessibility of health services,[21] availability of green spaces,[25] presence of tobacco and alcohol vendors,[23] social capital, and social disorder.[24]

Few studies have explored the association between neighborhood characteristics and T2D comorbidity in SMI, despite the public health burden and the plausibility of such associations.[26] Individuals with SMI are more likely to live in and be exposed to neighborhood environments that exacerbate T2D risk such as higher concentration of fast food outlets, lack of health care resources, and unsafe environments due to their lower socioeconomic status.[27,28] These contextual features may compound the experiences of psychosocial stress and encourage participation in adverse health behaviors such as unhealthy eating, physical inactivity, and excess weight gain, all of which can contribute to T2D risk.[18,27] We recently reported a statistically significant association between SMI-T2D comorbidity and neighborhood-level socioeconomic disadvantage.[29] One of the plausible explanations for the higher SMI-T2D comorbidity risk in disadvantaged neighborhoods may be the disproportionate availability of neighborhood resources in more disadvantaged neighborhoods as posited by the social determinants of health model.[30] For example, disadvantaged neighborhoods may lack access to fresh produce and be dominated by fast food and convenience stores, making the latter the easily available food option.[31] Similarly, disadvantaged neighborhoods might lack an environment conducive to physical activity.[1] Further exploration and identification of specific neighborhood-level characteristics is required to advance our understanding of T2D comorbidity in SMI and the possible associations neighborhood environments might have with this comorbidity. Understanding these associations may also help us develop integrated policies or place-based interventions that promote healthier environments to reduce the higher burden of T2D in individuals with SMI. There is, however, little evidence in the peer reviewed literature regarding the implementation and evaluation of such neighborhood-level integrated strategies on individuals with mental illness.

In this study, we aimed to investigate the associations of neighborhood environments with T2D comorbidity in individuals with SMI. A number of neighborhood indicators of T2D risk previously identified in the literature were analyzed. We specifically proposed to examine the association of 5 contextual neighborhood factors with SMI-T2D comorbidity: (1) neighborhood-level crime, (2) access to health care services, (3) availability of green spaces, (4) availability of fast food outlets, and (5) neighborhood-level obesity.[1,7,15,18,32-34]

Methodology

Study Design and Setting

This cross-sectional, multilevel study was conducted in Illawarra and Shoalhaven regions of New South Wales (NSW), Australia. The study site encompassed 4 local government areas of Kiama, Shellharbour, Shoalhaven, and Wollongong, and had an estimated resident population of 368 604 people at the time of the 2011 Australian Census of Population and Housing.[35] State suburbs were used as proxies for neighborhoods in this study as it was the smallest unit at which outcome data were available. State suburbs are the Australian Bureau of Statistics (ABS) approximation of suburbs gazetted by the Geographical Names Board of NSW.[36] The Illawarra-Shoalhaven region is composed of 167 suburbs with an average population of 2207 residents in 2011.[35] The University of Wollongong and Illawarra Shoalhaven Local Health District Human Research Ethics Committee granted ethical approval for this study (protocol number 2017/428).

Individual-Level Data and the Outcome variable

The individual-level data utilized in this study were extracted from the Illawarra Health Information Platform (IHIP), a research partnership established between Illawarra Shoalhaven Local Health District (ISLHD) and University of Wollongong for providing de-identified ISLHD data to researchers. Data extraction was based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM), and covered the period from 2010 to 2017. Eligibility criteria required a primary or additional diagnosis of schizophrenia (F20), other nonaffective psychosis (F22-F29), bipolar disorder (F30, F31), major depression (F32, F33) or other affective disorders (F34, F39) in the inpatient records of ISLHD. The outcome variable was SMI-T2D comorbidity, which was defined as having a T2D principal or stay diagnosis (E11) in people with SMI. Comorbidity details were extracted as either present or absent along with each record with an SMI diagnosis. We restricted our analysis to individuals with SMI who were 18 years and over. Individuals were excluded from the analysis if they lived outside the Illawarra-Shoalhaven (n = 50) or had missing information (n = 291). Consequently, the final

sample consisted of 3816 individuals with a diagnosis of SMI, of whom 463 (12.3 %) had a T2D comorbidity.

Neighborhood-Level Data

Our study focused on 5 neighborhood-level variables: (1) neighborhood-level crime, (2) access to health care services, (3) neighborhood-level obesity, (4) availability of green spaces, and (5) availability of fast food outlets. The selection of explanatory variables included in this analysis was somewhat restricted by data availability. Obesity was used as a contextual variable in this analysis as the information on individual-level obesity was not available for the study sample. Moreover, neighborhood environments are reported to provide cues that support social norms defining individuals' healthy behaviors, which can be compromised in a higher obese neighborhoods.[37] Hence the contextual effect of neighborhood level obesity may be informative in determining the T2D risk in SMI.

Annual area-level crime counts were obtained from the NSW Bureau of Crime Statistics and Research for the period 2010 to 2017. Crime types considered were nondomestic violent assaults, homicides, malicious damage to properties, abduction and kidnapping, robbery, and theft. Crime counts per neighborhood were expressed as rates per 1000 people using estimated resident populations from the 2011 Australian Census of Population and Housing.[35] Health care services data were extracted from the National Health Service Directory (NHSD) available from the Australian Urban Research Infrastructure Network (AURIN) portal for the year 2016.[38] To assess the availability of primary care, hospital, and mental health services in Illawarra-Shoalhaven, we used the 2-step floating catchment area method (2FSCA) that explicitly considers health care service supply and population demands and their interactions within a catchment.[39] In the first step, a 15-km distance catchment, corresponding to 30 minutes of travel time[40] was placed around each health care service provider, and a provider to population ratio was computed and assigned to these health care facilities. The population of the entire suburb is included in these calculations if its centroid falls within a health service catchment. In the second step, a similar floating catchment was placed over the suburb centroid and all health care services falling in the area were identified. Accessibility was computed by summing all provider to population ratios contained within the catchment. This method has been widely used in health care access research.[40,41]

Green space data were obtained from the AURIN portal and were available for 2018 only.[42] Data included green areas such as parks, reserves, national parks, conservation areas, forest reserves, recreational areas, and other open spaces. We used the proportion of green space per suburb to assess the degree of exposure to green space. Neighborhood level obesity was operationalized as percentage of population obese (body mass index [BMI] $\geq$30 kg/m^2) in each neighborhood.[43] BMI data were extracted from Southern IML Research (SIMLR) Study database for the period 2010 to 2014. The SIMLR Study is a longitudinal, community-derived cohort comprising a near-census of data collected from individuals aged 18 years and older in Illawarra-Shoalhaven, while presenting for private pathology testing.[44] Finally, fast food data were sourced from Open Street Map,[45] company websites and the Yellow Pages,[46] and were extensively cross-checked and verified. We defined fast food outlets as service establishments that sell quickly prepared food with payment made prior to receiving food and with little table service.[47] A population-scaled measure of fast food density was derived as the number of outlets per 10 000 people, which was computed using the estimated resident populations from the 2011 Australian Census of Population and Housing.[35]

All neighborhood variables, except fast food density, were converted from their continuous form into quintiles, where Q1 represents the highest availability and Q5 the lowest. Fast food data were collapsed into a binary scale as there were many suburbs with zero outlets. The quintiles were then assigned to individual records based on their suburb of residence.

Covariates

Individual level covariates comprised age at most recent admission, gender, and country of birth. Age was categorized as 18-44, 45-65, and 65+ years. Gender was categorized as male or female. Country of birth was grouped based on the *Standard Australian Classification of Countries* produced by the Australian Bureau of Statistics.[48] The Index of Relative Socioeconomic Disadvantage (IRSD) from the 2011 Socioeconomic Indexes for Areas product[49] was included in the analysis as a neighborhood-level covariate, as previous research had reported its association with SMI-T2D comorbidity.[29] The IRSD is an aggregate measure of the socioeconomic disadvantage for areas computed on the basis of 17 variables, including education, income, occupation, unemployment, housing type, overcrowding, and English proficiency. IRSD scores were classified into quintiles in this study.

Statistical Analysis

Descriptive analysis was conducted, and variable distributions assessed. A two stage modeling approach was used, whereby a series of single exposure multilevel models were run in the first stage followed by multi-exposure models in the second stage. Separate multilevel models were run in the first stage for each of the neighborhood variables to identify the specific associations between neighborhood features and

SMI-T2D comorbidity. Three models were fit for each of the 5 neighborhood variables and T2D comorbidity in SMI, accounting for neighborhood-level clustering. The first model was unadjusted; the second adjusted for individual-level variables (age, gender, country of birth); and the third expanded model 2 with adjustment for neighborhood-level IRSD.

In the second stage, a series of multivariable random intercept logistic regression models were then calculated: first with no predictors; then with individual predictors only; and finally, with both individual- and neighborhood-level characteristics. This approach was used to estimate the intraclass correlation coefficient (ICC), and also to identify the potential confounding between various neighborhood characteristics. The ICC is the proportion of variance in the outcome variable attributed to differences between individuals in different neighborhoods as opposed to differences between individuals within the same neighborhood and was calculated by the latent variable method.[50,51] The proportion of the neighborhood-level variance explained by different neighborhood variables was also calculated.[51] The sensitivity of results to including neighborhood-level obesity was evaluated by refitting the final model excluding this variable. All neighborhood- and individual-level interactions were also examined to investigate potential cross-level effect modifications. Descriptive and multilevel analysis was completed using R (version 3.5)[52] and the statistical significance was set at $P < .05$.

Results

The study population consisted of 3816 individuals aged 18 years and older, of whom 463 (12.3%) had a SMI-T2D comorbidity (Table 1). Individuals with comorbidity were mostly females (52.9%), aged 65 years and older (38.4%), and born in Australia (73.2 %). The distributions of neighborhood variables are also given in Table 1. Variance inflation factors (VIF) were computed to ensure that multicollinearity did not bias the analysis.[53] On assessing all neighborhood variables, none showed evidence of multicollinearity (VIF <3).

Table 2 presents single-exposure (stage 1) associations between neighborhood features and SMI-T2D comorbidity. Only area level crime rates were significantly related to SMI-T2D comorbidity after adjusting for individual factors and neighborhood-level socioeconomic disadvantage (Table 2, model 3): Living in areas with a higher crime rate was associated with higher odds of SMI-T2D comorbidity compared with living neighborhoods with a lower crime rate (odds ratio [OR] 2.48, 95% CI 0.91-6.74). No significant associations were observed between health care access, neighborhood obesity, green spaces or fast food availability, and the odds of SMI-T2D comorbidity (Table 2, model 3).

When all neighborhood variables were included in multivariable models with individual-level covariates (see Table 3, model 4), area-level crime remained significantly associated with SMI-T2D comorbidity. The odds ratio for the highest crime quintile increased compared with the single exposure models and remained statistically significant (OR 2.78, 95% CI 1.02-7.57, $P = .002$). The ICC for the null model was 0.029, indicating that 2.9% of the variance in SMI-T2D comorbidity was attributable to between neighborhood differences. Addition of all the neighborhood features in model 4 (Table 3) accounted for 87.76% of between area variance and the ICC for this model was reduced to 0.004, indicating that the majority of residual variance in SMI-T2D risk was attributed to within-neighborhood rather than between-neighborhood differences. Sensitivity analysis excluding neighborhood-level obesity did not change the results substantially (Supplementary Material 1). There was no evidence of interaction between individual- and area-level variables (Supplementary Material 2).

Discussion

We examined associations between characteristics of neighborhood environments and the likelihood of SMI-T2D comorbidity. The results indicate that approximately 3% of the total variance in SMI-T2D comorbidity was attributed to neighborhood characteristics. The neighborhood variables included in this study accounted for approximately 45% of this neighborhood variation and neighborhood socioeconomic disadvantage accounted for an additional 17%. A statistically significant positive association was observed between area-level rates of crime and SMI-T2D comorbidity independent of individual-level characteristics and neighborhood-level socioeconomic disadvantage. No significant associations were observed between the other 4 neighborhood variables included: access to health care services, neighborhood-level obesity, availability of green spaces, and availability of fast food restaurants and SMI-T2D comorbidity, suggesting that it is unlikely that these neighborhood features have a large influence on SMI-T2D comorbidity.

Even though modest amounts of neighborhood variance in SMI-T2D comorbidity was reported in this study, noting that the whole population is impacted by any small changes to reduce the neighborhood disparities is important. As Geoffrey Rose has pointed out, population-based approaches have the potential to shift the risk distribution of the entire population in a favorable direction and are considered more effective in reducing the disease burden than a "high-risk" approach in which measures are targeted only to individuals with substantially higher risk.[54]

This is one of the few studies to investigate the relationship between neighborhood features and SMI-T2D

Table 1. Descriptive Characteristics of the Study Population.

Variables	Individuals with SMI (n = 3816), n (%)	Individuals with SMI + T2D (n = 463), n (%)	% comorbidity
Individual variables			
Gender			
Female	1848 (48.4)	245 (52.9)	13.3 (12.2-14.4)
Male	1968 (51.6)	218 (47.1)	11.1 (10.1-12.1)
Age, years, mean (SD)	43.6 (18.5)	58.8 (15.7)	
Age, years			
18-44	1961(51.4)	92 (19.9)	4.7 (4.0-5.4)
45-65	1213 (31.8)	193 (41.7)	15.9 (14.7-17.1)
65+	642 (16.8)	178 (38.4)	27.7 (26.3-29.1)
Country of birth			
Australia	3104 (81.3)	339 (73.2)	10.9 (9.9-11.9)
Oceania excluding Australia	74 (1.9)	12 (27.9)	16.2 (15.0-17.4)
UK and Ireland	212 (5.6)	35 (7.6)	16.5 (15.3-17.7)
Western Europe	137 (3.6)	29 (6.3)	21.2 (19.9-22.5)
Eastern and central Europe	125 (3.3)	29 (6.3)	23.2 (21.9-24.5)
Northeast Asia	17 (0.45)	0 (0.0)	0.0 (0.0-18.4)
Southeast Asia	51 (1.3)	6 (1.3)	11.8 (10.8-12.8)
Central and South Asia	16 (0.4)	3 (0.6)	18.8 (17.6-20.4)
Middle East and North Africa	39 (1.0)	9 (1.9)	23.1 (21.8-24.4)
Sub-Saharan Africa	20 (0.5)	0 (0.0)	0.0 (0.0-16.1)
Americas	21 (0.6)	1 (0.2)	4.8 (4.1-5.5)
Neighborhood variables			
IRSD scores, mean (SD)	940.5 (82.1)	934.1 (88.3)	
IRSD			
Q1 (highest disadvantage)	1752 (45.9)	229 (49.5)	13.1 (12.0-14.2)
Q2	943 (24.7)	120 (25.9)	12.7 (11.6-13.8)
Q3	620 (16.2)	75 (16.2)	12.1 (11.1-13.1)
Q4	362 (9.5)	34 (7.3)	9.4 (8.5-10.3)
Q5 (lowest disadvantage)	139 (3.6)	7 (1.5)	5.1 (4.4-5.8)
Area-level crime, mean (SD)	831.4 (615.5)	833.9 (557.2)	
Area level crime			
Q1 (highest crime)	1900 (49.8)	270 (58.3)	14.2 (13.1-15.3)
Q2	847 (22.2)	105 (22.7)	12.4 (11.4-13.5)
Q3	655 (17.2)	62 (1.6)	9.5 (8.6-10.4)
Q4	317 (8.3)	20 (0.5)	6.3 (5.5-7.1)
Q5 (lowest crime)	97 (2.5)	6 (0.2)	6.2 (5.4-7.0)
Access to health care, mean (SD)	2.2 (3.6)	2.2 (3.6)	
Access to health care			
Q1 (highest access)	833 (21.8)	114 (24.6)	13.7 (12.6-14.8)
Q2	968 (25.4)	98 (21.2)	10.1 (9.1-11.1)
Q3	1339 (35.1)	160 (34.6)	11.9 (10.9-12.9)
Q4	592 (15.5)	82 (17.7)	13.9 (12.8-15.0)
Q5 (lowest access)	84 (2.2)	9 (1.9)	10.7 (9.7-11.7)
Green space availability, mean (SD)	14.3 (18.0)	13.1 (17.5)	
Availability of green spaces			
Q1 (highest availability)	93 (2.4)	10 (2.2)	10.8 (9.8-11.8)
Q2	341 (8.9)	37 (8.0)	10.9 (9.9-11.9)
Q3	688 (18.0)	82 (17.7)	12.0 (11.0-13.3)
Q4	742 (19.4)	82 (17.7)	11.05 (10.5-12.6)
Q5 (lowest availability)	1952 (51.2)	252 (54.4)	12.9 (11.1-13.1)

(continued)

Table 1. (continued)

Variables	Individuals with SMI (n = 3816), n (%)	Individuals with SMI + T2D (n = 463), n (%)	% comorbidity
Neighborhood obesity, mean (SD)	17.9 (3.8)	18.0 (3.8)	
Neighborhood obesity			
Q1 (highest obesity)	1444 (37.8)	175 (37.8)	12.1 (11.1-13.1)
Q2	974 (25.5)	118 (25.5)	12.1 (11.1-13.1)
Q3	873 (24.0)	100 (22.4)	11.5 (10.4-12.5)
Q4	446 (10.6)	64 (13.0)	14.3 (13.2-15.4)
Q5 (lowest obesity)	79 (2.1)	6 (1.3)	7.6 (6.8-8.4)
Fast food availability, mean (SD)	9.3 (8.1)	10.0 (9.8)	
Fast food availability			
Available (>0)	3157 (82.7)	380 (82.1)	12.0 (10.8-13.0)
Not available (0)	659 (17.3)	83 (17.9)	12.6 (11.6-13.7)

Abbreviation: ISRD, Index of Relative Socioeconomic Disadvantage.

comorbidity. To the best of our knowledge, this is also the first report of a direct association between objectively measured area-level crime and T2D risk in individuals with SMI. Our results parallel those of a recent study from the United States, which reported an increased odds of depression and T2D comorbidity in neighborhoods with higher perceived neighborhood problems such as violence.[55] Other research has also connected perceived neighborhood crime rate to independent T2D incidence[32,56] as well as to the risk factors of T2D such as psychological distress, lower physical activity, and obesity.[18,19,57,58] Furthermore, persistent exposure to fear and stress are proposed to alter immune system response and activate the hypothalamic pituitary adrenal axis accelerating the development of T2D.[1,59]

In contrast to previous studies on independent T2D risk, we identified no significant association between SMI-T2D comorbidity and neighborhood resources such as health care access, fast food availability, and green spaces. However, one previous study by Kirkpatrick et al[60] had reported increased T2D risk in psychosis patients independent of access to care. One potential explanation for these null findings could be that individuals with SMI may have trouble changing an unhealthy lifestyle despite the availability of resources due to their psychosocial disability and cognitive impairment.[61,62] For example, lower physical activity could be due to negative symptoms and social isolation, and neighborhood level green space may not be a relevant resource for physical activity in individuals with SMI. Similarly, negative and psychotic symptoms can be barriers to accessing health care services despite availability.[4,60] The null results may also be attributable to differences in study design, neighborhood measures assessed, the way in which constructs were evaluated (eg, density vs distance, quantity vs quality), and the population examined. With regard to health care access, it should be noted that Australia has a national health care scheme (Medicare), envisioned to deliver the most equitable and efficient health care access at reduced or no cost.[63] This along with several Australian Government initiatives to improve health care access for people with mental illness may have resulted in decreased inequities in health care access for this population. It is unlikely for an effect to be detected without variations in neighborhood exposures. The lack of association of SMI-T2D comorbidity with health care access may also be due to the inefficiency of current primary care interventions designed for general population in reaching disadvantaged groups such as individuals with SMI, as suggested by a systematic review by Glazier et al.[64] Hence individuals with SMI may require additional support to utilize the available resources to achieve the same effect realized by individuals without SMI. Further research is needed to draw definitive conclusions.

Strengths and Limitations

Strengths of our study include a large sample of clinically coded individuals with SMI, assessment of multiple environment features, use of objectively measured neighborhood data collected from different sources, and multilevel analysis. Limitations include the cross-sectional design, which prevents us from drawing causal inferences. Individual-level data used in this study were sourced only from inpatient mental health records and did not consider outpatient and private practice records. The Australian National Surveys of Psychosis indicates that 45.6% to 62.9% of people with SMI reported ≥1 hospital admission for any reason in the previous 12 months.[65] As such, our 8-year data collection period should have provided a reasonable coverage of the study population. It is also possible that our results are influenced by temporal misalignment as neighborhood-level data were collected for different time periods due to the nonavailability of historical data on these

Table 2. Results of Single Exposure Multilevel Logistic Regression.[a]

	Model 1		Model 2		Model 3	
Variable	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Area-level crime	1.17 (0.97-1.41)	.002	1.19 (0.99-1.44)	.013	1.02 (0.82-1.28)	.032
Area-level crime						
Q1 (highest crime)	2.90 (1.21-6.97)		3.08 (1.28-7.44)		2.48 (0.91-6.74)	
Q2	2.30 (0.94-5.60)		2.59 (1.06-6.35)		2.11 (0.77-5.76)	
Q3	1.59 (0.65-3.94)	<.001	1.61 (0.65-3.99)	<.001	1.27 (0.46-3.49)	.001
Q4	1.00 (0.37-2.66)		1.17 (0.43-3.13)		1.02 (0.36-2.83)	
Q5 (lowest crime)	1.00		1.00		1.00	
Access to health care	1.0 (0.89-1.12)	.984	0.99 (0.88-1.11)	.87	1.05 (0.94-1.19)	.385
Access to health care						
Q1 (highest access)	1.34 (0.61-2.94)		1.46 (0.66-3.21)		1.68 (0.76-3.71)	
Q2	0.96 (0.43-2.11)		1.05 (0.47-2.33)	.386	1.11 (0.47-2.33)	.241
Q3	1.18 (0.54-2.57)		1.27 (0.58-2.78)		1.35 (0.62-2.96)	
Q4	1.39 (0.62-3.09)		1.42 (0.63-3.16)		1.39 (0.63-3.09)	
Q5 (lowest access)	1.00		1.00		1.00	
Availability of green spaces	0.91 (0.81-1.03)	.137	0.90 (0.79-1.00)	.064	0.94 (0.83-1.08)	.378
Availability of green spaces						
Q1 (highest availability)	0.74 (0.36-1.52)		0.72 (0.34-1.50)		1.08 (0.50-2.32)	
Q2	0.76 (0.50-1.18)		0.73 (0.47-1.12)		0.88 (0.56-1.37)	
Q3	0.82 (0.58-1.16)	.318	0.81 (0.58-1.14)	.285	1.02 (0.70-1.47)	.511
Q4	0.71 (0.50-1.02)		0.73 (0.52-1.02)		0.76 (0.54-1.07)	
Q5 (lowest availability)	1.00		1.00		1.00	
Neighborhood obesity	1.05 (0.93-1.19)	.39	1.05 (0.93-1.19)	.426	1.00 (0.99-1.00)	.384
Neighborhood obesity						
Q1 (highest obesity)	1.85 (0.76-4.53)		1.65 (0.66-4.10)		1.19 (0.48-2.97)	
Q2	1.66 (0.67-4.10)		1.53 (0.61-3.83)		1.39 (0.56-3.49)	
Q3	1.60 (0.64-3.99)	.481	1.47 (0.59-3.70)	.532	1.54 (0.60-3.96)	.157
Q4	2.05 (0.81-5.17)		1.95 (0.75-4.99)		2.03 (0.79-5.26)	
Q5 (lowest obesity)	1.00		1.00		1.00	
Fast food availability	1.08 (0.98-1.20)	.129	1.07 (0.96-1.19)	.215	1.03 (0.92-1.16)	.544
Fast food availability						
Not available (0)	1.01 (0.75-1.36)	.927	1.08 (0.80-1.44)	.617	1.29 (0.91-1.75)	.107
Available (>0)	1.00		1.00		1.00	

[a]Model 1: Unadjusted. Model 2: Adjusted for individual-level variables. Model 3: Adjusted for individual-level variables and neighborhood Index of Relative Socioeconomic Disadvantage. Odds ratios for continuous variables expressed as odds per standard deviation.

Table 3. Multivariable Regression Analysis.[a]

	Model 1		Model 2		Model 3		Model 4	
Variables	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
Individual variables								
Sex								
Female			1.00		1.00		1.00	
Male			0.95 (0.78-1.17)	.658	0.96 (0.78-1.17)	.687	0.96 (0.78-1.18)	.685
Age (years)								
18-44			1.00		1.00		1.00	
45-65			3.79 (2.91-4.93)		3.78 (2.90-4.92)		3.77 (2.88-4.92)	
65+			7.68 (5.77-10.23)	<.001	7.82 (5.87-10.42)	<.001	7.87 (5.89-10.51)	<.001
Country of birth								
Australia			1.00		1.00		1.00	
Oceania excluding Australia			1.57 (0.81-3.03)		1.53 (0.79-2.97)		1.57 (0.81-3.04)	
UK and Ireland			0.84 (0.57-1.26)		0.88 (0.59-1.31)		0.85 (0.57 -1.26)	
Western Europe			0.99 (0.63-1.54)		0.97 (0.62-1.52)		0.99 (0.63 -1.55)	
Eastern and central Europe			1.30 (0.82-2.05)		1.30 (0.82-2.06)		1.38 (0.87-2.19)	
Southeast Asia			1.30 (0.53-3.19)		1.30 (0.52-3.19)		1.25 (0.51-3.07)	
Central and South Asia			2.03 (0.53-7.82)		2.13 (0.56-8.10)		2.09 (0.55-7.98)	
Middle East and North Africa			1.84 (0.83-4.09)		1.87 (0.84-4.16)		1.94 (0.87-4.32)	
Americas			0.42 (0.06-3.25)	.137	0.41 (0.05-3.15)	.149	0.39 (0.05-3.04)	.145
Neighborhood variables								
IRSD quintiles								
Q5 (least disadvantaged)					1.00		1.00	
Q4					1.87 (0.77-4.53)		1.57 (0.59 -4.19)	
Q3					2.67 (1.14-6.15)		1.73 (0.65-4.67)	
Q2					2.92 (1.28-6.67)		1.97 (0.72-5.35)	
Q1 (most disadvantaged)					3.20 (1.42-7.20)	0.008	1.96 (0.69-5.51)	.69
Area-level crime								
Q5 (lowest crime)								
Q4							1.00	
Q3							0.97 (0.34-2.73)	
Q2							1.56 (0.57-4.27)	
Q1 (highest crime)							2.20 (0.81-5.99)	
							2.78 (1.02-7.57)	0.001
Variance of random effects								
T^2	0.098		0.073		0.056		0.012	
PCV	Reference		25.50%		42.90%		87.76%	
ICC	0.029		0.0217		0.017		0.004	

Abbreviations: IRSD, Index of Relative Socioeconomic Disadvantage; PCV, Proportion Change in Variance; ICC, Intraclass Correlation Coefficient; T^2, Area level variance

[a]Only significant neighborhood variables reported. Model 1: Null model with suburban-level random effect. Model 2: Model 1 + individual-level factors. Model 3: Model 2 + neighborhood-level IRSD quintiles. Model 4: Model 3 + neighborhood variables.

neighborhood variables. Individual socioeconomic status, which is often used in neighborhood studies, was also not available for inclusion in this analysis. Likewise, information regarding the level of diabetes and SMI control was not available for inclusion in this study. In addition, multilevel modeling approach employed in this study may be limited in its ability to provide optimal information on the spatial distribution of outcomes, as it fragments space into arbitrary administrative areas and ignores the spatial association between them.[66] However, Moran's *I* statistics of area-level

residuals did not reveal spatial autocorrelation unaccounted by multilevel models used in this study,[67] indicating further spatial exploration is unwarranted. We also acknowledge the limitation of using neighborhood obesity as a proxy for neighborhood cues for obesogenic environment. However, sensitivity analysis excluding the variable did not alter the results substantially.

Conclusions

T2D comorbidity in SMI is a major public health issue. While many studies investigating this association looked at the individual level factors, we examined the added influence of neighborhood contextual environments on SMI-T2D comorbidity. We observed that individuals with SMI residing in areas with higher crime rates were more likely to report T2D comorbidity compared to individuals with SMI residing in lower crime rate areas, even after controlling for individual-level variables and neighborhood-level disadvantage. The study provides a case for primary and community health stakeholders to be mindful of the neighborhood discrepancies in SMI-T2D comorbidity. The findings support targeted neighborhood level initiatives aimed at individuals with SMI living in high-crime neighborhoods in order to reduce the public health burden imposed by SMI-T2D comorbidity. Overall, the study suggests that the mechanisms of neighborhood influence on SMI-T2D are highly complex. Further research is needed incorporating longitudinal study designs, data from different geographic locations, more rigorous measurements, variables not included in this study and mediation analysis to further understand the mechanisms linking neighborhoods and T2D comorbidity in SMI, with the aim of informing policies and practices that may reduce the burden.

Acknowledgments

We thank Illawarra Health Information Platform (IHIP), a research partnership established between the Illawarra Shoalhaven Local Health District (ISLHD) and the University of Wollongong (UOW) for providing the data used in this study (https://ahsri.uow.edu.au/chrisp/ihip-data/index.html). We also thank Southern IML Pathology and staff for providing the BMI data from the SIMLR (Southern IML Research) cohort study for use in this research. Southern IML pathology are the owners of BMI data contained within this publication and Illawarra Health and Medical Research Institute (IHMRI) is the custodian facilitating access to these data (https://www.ihmri.org.au/research-projects/simlr-cohort-study/)

Author Contributions

RW undertook literature review, contributed to the research design, analysed and interpreted the data and drafted the manuscript. AB, XF, DM and NP supervised the project, contributed to the study design, helped with the interpretation of results, critically reviewed the manuscript and helped draft the final version for submission.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was conducted with the support of Australian Government Research Training program scholarship and Illawarra Shoalhaven Local Health District–University of Wollongong combined scholarship.

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Supplemental Material

Supplemental material for this article is available online.

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