Examining the association between urbanicity and first episode psychosis in Chile

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Submitted in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy
under the Executive Committee
of the Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY

2024

Abstract

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This dissertation sought to characterize the association between urbanicity and incidence of

first-episode psychosis (FEP) in Chile by using data from national registries, including a national

FEP registry, as well as other health and social databases. Numerous large, well-controlled

studies from Northern European countries (e.g., Denmark) have found that being born or

brought up in urban environments increases the odds of developing psychosis. Given the

strength and consistency of these findings over decades, the urbanicity-psychosis association is

considered one of the fundamental epidemiologic findings on environment and psychosis, and

full-fledged research programs have been examining potential mechanisms. Yet it now appears

that the association may not be universal. Studies from some European countries, Latin

America, and China have reported null results. These findings have started to change our

understanding of the urbanicity-psychosis association and have raised important questions

regarding how the association works in understudied, lesser-resourced settings. Chile, with its

unique juxtaposition of substantial infrastructure (national registries) and shared challenges with

other Latin American countries, offers an unprecedented context for developing such research.

Accordingly, the specific aims of this dissertation were to 1) conduct a qualitative systematic

literature review on the definitions of urbanicity and community-level social factors in the context

of psychosis research, 2) examine whether urbanicity at birth and at admission is associated

with increased risk of FEP, and 3) examine the moderation effects of social deprivation in the

association between urbanicity and incidence of FEP.

Introduction

This dissertation sought to characterize the association between urbanicity and incidence of first-episode psychosis (FEP) in Chile by using data from national registries, including a national FEP registry, as well as other health and social databases. Except for Chile, recently classified as a high-income country (HIC), no country from Latin America has a national FEP registry. Psychiatric registries are especially useful for psychosis etiologic research because most people with psychosis are treated and therefore enter these registries in HICs, which have been central to North European studies of urbanicity and psychosis. Hence, the Chilean FEP registry, alongside other Chilean national databases, provides a unique opportunity to advance our understanding of the association between urbanicity and risk of psychosis (henceforth, the urbanicity-psychosis association) in a Latin American context.

Given the societal impact of mental health conditions on individual functionings and capabilities, a human development framework is potentially useful for understanding their contextual determinants and implications (Marmot, 2018). Therefore, I have used the Capability Approach, a well-known theoretical framework on development, equity, and well-being (Sen, 1985, 1999), to guide this dissertation, interpret its results, and discuss their implications. This approach emphasizes the importance of people's functionings and capabilities to have the kind of lives they value and make choices that enable them to achieve their own goals and aspirations considering contextual factors and barriers (Nussbaum, 2011). Following Amartya Sen's seminal work (1985, 1999), functionings are the various things a person can do or be that are of value – are meaningful – to them, such as being healthy, educated, having access to clean water, or participating in cultural and social activities. Capabilities refer to a person's ability to achieve these functionings within their social context.

The capabilities approach has been proposed as a way to advance the recovery and social models in mental health (Hopper, 2007; 2012; Wallcraft & Hopper, 2015). Wallcraft and Hopper (2015) argue that the capabilities approach provides a robust and practical framework

for examining the role of structural constraints on individuals with mental conditions—often overlooked in enhanced models such as the psychosocial model. The approach also helps to interpret the significance of agency and freedom in specific contexts and to involve individuals with mental health conditions in the creation and assessment of mental health outcomes. While initial work has emerged in community mental health (Sacchetto et al., 2018), including the development and adaptation of measures for mental health and housing services (Sacchetto et al., 2016; Greenwood et al., 2022), the capabilities approach remains underutilized in examining how structural elements such as urbanicity and social disadvantage may increase and moderate the risk of mental health issues. Hence, the use of this framework could reveal important risk factors and illuminate prevention efforts.

In principle, urban areas should offer better prospects for health with better infrastructure and access to health care. However, the so-called "urban advantage" is not equally distributed and marginalized groups usually do not enjoy it. Specifically, people exposed to socially and materially deprived settings in urban areas face major barriers to develop capabilities (Vassos et al., 2012). Drawing from the capability approach, I propose that urbanicity is not merely a geographic or an administrative concept but a dynamic, socially embedded, phenomenon that deeply influences the capabilities and choices available to individuals. In this context, I argue that we need to understand urbanicity not just as a physical setting but as a space that offers (or limits) the development of certain capabilities, such as the ability to have a healthy life and access educational and employment opportunities (Nussbaum, 2011). These limitations on capability development in urban settings may increase the risk of various health and mental health conditions, including psychosis.

Numerous large, well-controlled studies from Northern European countries (e.g., Denmark) have found that being born or brought up in urban environments increases the odds of developing psychosis. Given the strength and consistency of these findings over decades, the urbanicity-psychosis association is considered one of the fundamental epidemiologic

findings on environment and psychosis, and full-fledged research programs have been examining potential mechanisms. Yet it now appears that the association may not be universal.

Studies from some European countries (e.g., Italy, Spain), Latin America (e.g., Chile, Brazil), and China have reported null results (Del-Ben et al., 2019; González-Valderrama et al., 2022; Jongsma et al., 2018; Long et al., 2014). These findings have started to change our understanding of the urbanicity-psychosis association and have raised important questions regarding how the association works in understudied, lesser-resourced settings. Moreover, when examining the evidence on the urbanicity/psychosis association, we should acknowledge the variation in how urbanicity is defined and operationalized across studies, especially when comparing studies from Northern Europe with those from other regions. We need more research to clarify these definitional variations and identify the components of urban/rural life that relate to psychosis. Chile, with its unique juxtaposition of substantial infrastructure and shared challenges with other Latin American countries, offers an unprecedented context for developing such research.

Chile is world-renowned for its longstanding tradition in implementing health and mental health reforms. There are two recent reforms that ensure the feasibility of a rigorous study. First, since 2005, government legislation mandates that any person identified by health services as having FEP must be recorded in a national FEP registry. This registry records routine information including the number of people with FEP identified annually in every locale of Chile, as well as several sociodemographic variables such as age, gender, socioeconomic status, place of admission, and place of residence. Additionally, there is a mandate for free treatment for those identified, and a protocol for a 6-month period to confirm diagnoses, acknowledging that initial diagnoses may evolve over time. This approach not only underscores the commitment to care but also enhances the reliability of the registry data, as it considers a refinement process. Second, as part of a larger reform in health and social services, the Chilean government has started to standardize and link several national databases. For this dissertation,

I have used, in addition to the FEP registry, the Birth and Death registry, including data on parental antecedents and place of birth. These data can be used to minimize potential confounding at the individual-level and examine the moderation effects of social deprivation as reported in previous studies from Northern Europe.

A previous preliminary study did not detect an association between urbanicity and psychosis in Chile (González-Valderrama et al., 2022). This study was, however, based on incomplete data, and did not have access to the rich data sources that were used in the present study. Thus, several limitations may have biased its results and precluded its conclusions. First, the authors only used approximate diagnosis for measuring the outcome (i.e., including both "suspected" and "confirmed" cases). Since over 20-30% of the "suspected" cases end up not receiving a FEP diagnosis (Markkula et al., 2011), measurement error was likely. Second, for the prior study the FEP registry was not yet linked to the other registries used here. Consequently, the authors did not have data on potential confounders. In addition, they only had the records of place of admission from the FEP registry; for place of birth the linkage to the Birth/Death registry is required. Third, they used only one approach to measuring urbanicity based on population density which has been used in some previous studies but does not correspond to the more comprehensive definition of rural/urban used in this study. All these points are addressed by the current thesis and discussed in more detail later.

Accordingly, the specific aims of this dissertation were to:

Aim 1. Conduct a qualitative systematic literature review (Butler, Hall, & Copnell, 2016) on the definitions of urbanicity and community-level social factors (i.e., social fragmentation) in the context of psychosis research.

Aim 2. Examine whether urbanicity at birth and at admission is associated with increased risk of FEP.

Aim 3. Examine the moderation effects of social deprivation in the association between urbanicity and incidence of FEP.

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Defining urbanicity in the context of psychosis research: A qualitative systematic literature review

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Abstract

The association between urbanicity and psychosis has been extensively studied. Numerous studies have found that being born or raised in urban environments increases the odds of developing psychosis. From a Capability Approach perspective, highly populated, urban settings can limit the development of capabilities, such as having good mental and physical health. However, recent research suggests that this relationship may not be universal and could be context dependent. To deepen our understanding of the different concepts and measures of urbanicity and related community-level social factors in psychosis research, a qualitative systematic literature review (QSLR) was conducted, extracting information from studies published between 2000 and 2023. Sixty-one articles met the inclusion and exclusion criteria and were used in the thematic analysis. The analysis revealed that urbanicity lacked a single, coherent definition across studies and regions. Three major categories of themes emerged from the analysis: (a) Urbanicity comprises several interconnected constructs, (b) Urbanicity measurements vary between countries from the Global North and the Global South, and (c)

Urbanicity operates through key neighborhood-level mechanisms. Future research on urbanicity and psychosis should consider the potential limitations of urbanicity's conceptualization and operationalization and aim to address these limitations by focusing on contextual, historical, and community-level factors, utilizing locally validated measures, and employing mixed-method designs. Moreover, the Capability Approach could offer a nuanced framework for understanding how these multiple-level factors influence individual capabilities in urban environments and potentially increase the risk of psychosis.

Background

Numerous well-designed studies from Northern European countries (e.g., Denmark) have found that being born or raised in urban environments increases the odds of developing non-affective psychosis (Fett, Lemmers-Jansen, & Krabbendam, 2019; Krabbendam & van Os, 2005). The bulk of these studies relied upon psychiatric and other national registries. Given the strength and consistency of these findings over decades, the urbanicity-psychosis association is considered one of the fundamental epidemiologic findings on environment and psychosis (Kirkbride, Keyes, & Susser, 2018), and full-fledged research programs have been examining potential mechanisms.

Nevertheless, recent studies suggest that the association might be specific to Northern Europe (or similar contexts) rather than universal (Kirkbride et al., 2018). Recent studies in Southern Europe (e.g., Italy, Spain) have not found this association (Jongsma et al., 2018). Likewise, recent studies from the Global South (which refers broadly to the regions of Latin America, Asia, Africa, and Oceania) also do not support this association (Del-Ben et al., 2019; DeVylder et al., 2018; González-Valderrama et al., 2022). These studies from other regions have not used designs of comparable strength to those from Northern Europe. Limitations include small sample sizes and/or unreliable measures. With a few exceptions (Morgan et al., 2023), they have not used samples representative of a national or regional population. Thus,

whether or to what degree urbanicity is associated with psychosis outside contexts like Northern Europe remains an open question- and a crucial one for psychosis research (Kirkbride et al., 2018).

A limitation in all studies thus far is that the components of urban and rural life that could lead to a difference in psychosis risk have not yet been well characterized or shown to pertain across different countries. Studies from Northern Europe have investigated whether factors associated with high population density, such as social fragmentation or social deprivation, might represent aspects of the urban environment that partially explain the observed association. However, these concepts have been operationalized in various ways, and their measures tend to be incomplete (Krabbendam & van Os, 2005). Furthermore, few people in Northern Europe live in truly rural as opposed to semirural areas, and as a result, little conceptual or empirical work has been done on factors associated with rural (rather than semirural) living that might decrease or increase the risk of psychosis (Kirkbride et al., 2018). Outside Northern Europe, there are few theoretical or empirical studies of how population density corresponds to theoretical concepts of urban and rural that could be relevant to psychosis risk. For instance, Roberts et al. (2023), in three population-based studies using the same protocol (controls matched to incident help-seeking cases) and definition for urbanicity (degree of urbanization based on both population density and density of built-up areas) found that in Trinidad and Tobago urban versus rural categories were locally meaningful, but it was difficult to differentiate urban and rural as opposed to semirural in India and Nigeria. Also, in countries where much larger numbers of people live in remote rural areas, their living conditions could be quite different from those living in semirural areas in Northern Europe. For example, in several areas in Latin America, there are different age structures and social life where migration to wealthier urban areas left a residual population in rural areas (Tacoli, McGranahan, & Satterthwaite, 2015). Therefore, to advance this research area, we need stronger studies

outside Northern Europe, and a deeper understanding of what urban and rural, and semirural, living conditions signify.

Furthermore, some argue that relying solely on general indicators of urbanicity, such as population density, does not adequately consider the multifaceted aspects of urban living. Factors such as air quality, access to services, social interactions, and violence and crime collectively shape individuals' lived experiences. This is where the Capability Approach offers a nuanced framework for examining how various aspects of urbanicity interact with individual capabilities (i.e., the opportunity to achieve combinations of human functionings that the individual values – what a person is able to do or be) (Sen, 1985, 1999), thereby influencing mental health outcomes. The approach suggests that we should not focus solely on the presence or absence of a particular resource (e.g., health services), but on individuals' genuine freedoms to make choices that enhance their well-being or whether they are constrained by various urban factors (e.g., lack of use of services due to marginalization). For instance, 'social participation,' a capability often hindered in densely populated urban environments, is affected by factors like social fragmentation and isolation. The Capability Approach would not merely identify the reduction in social interactions but would extend the analysis to how this limitation affects an individual's ability to achieve well-being. Similarly, the capability for 'bodily integrity' might be compromised in urban settings due to higher crime rates or pollution, which in turn could have implications for mental health. This approach encourages a multifaceted analysis that goes beyond material conditions, examining how urban environments can either expand or constrain the crucial capabilities necessary for mental health.

Theories from various fields, including urbanism, architecture, geography, and social anthropology, can contribute valuable insights to characterize the multifaceted aspects of urbanicity. For example, Winz (2018) proposes an approach that focuses on ambiance and affective atmosphere, which captures the intricate and nuanced perceptual, sensory, and conscious experiences of individuals residing in diverse urban and semi-urban environments.

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Similarly, Söderström et al. (2016) suggest an experience-based approach that employs video elicitation and qualitative methods to attain a more detailed understanding of the relationship between the city and psychosis. Drawing evidence from these fields holds great potential to enhance future research in the epidemiology of psychosis.

This piece undertook a comprehensive, socioculturally sensitive analysis of different concepts and measures of "urban" living and related community-level factors, such as social deprivation and social fragmentation, in the context of psychosis research. I have conducted a qualitative systematic literature review (QSLR) (Butler, Hall, & Copnell, 2016) of studies published between 2000 and 2023. In contrast to narrative reviews, QSLRs use rigorous and transparent procedures to identify, evaluate, and interpret available research while reducing potential biases. QSLRs are particularly useful for synthesizing, contextualizing, and interpreting available evidence. To our understanding, no QSLRs focusing on extant definitions of urbanicity have been conducted to date, which may explain the lack of a more granulated and meaningful definition for this exposure in the literature. Moreover, different definitions for the exposure may affect the nature, direction, and strength of the urbanicity-psychosis association, especially in contexts where this line of research is emerging (e.g., the Global South) (Morgan et al., 2023). The present review fills this gap by examining the thematic components of extant definitions and contributing to the ongoing discussion of how urbanicity should be understood and measured in psychosis research.

Accordingly, my goals were to a) examine how urbanicity (in contrast to rural as well as to semirural areas) and related community-level social factors have been defined in the psychosis literature between 2000 and 2023 and b) identify and characterize core thematic categories underlying the definitions of urbanicity and related factors.

Method

I used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) to develop this review (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009).

First, a search of scientific reports was conducted using the following databases: PubMed,

Google Scholar, EBSCO, Ovid, Embase, and SciELO. Grey literature was searched using

databases such as OpenGrey (http://www.opengrey.eu/). I identified and distinguished countries

from the Global South versus the Global North following the United Nations (UN) taxonomy

(*World Urbanization Prospects The 2018 Revision*, 2019). I used the UN Geoscheme

Classification to group Northern European countries (i.e., Denmark, Estonia, Finland, Iceland,

Ireland, Latvia, Lithuania, Norway, Sweden, and the United Kingdom) and distinguished them

from other countries as most research conducted to date has been done in the former. I also

checked for cities and/or locales within the Global South (e.g., Sao Paulo) in case these were

mentioned in titles/abstracts instead of countries. Second, keywords in English, Spanish, and

Portuguese were used. I kept search terms broad to find relevant studies even when the

specific keywords "urbanicity" (or "semirural" or "rural") or "psychosis" were not mentioned in the

title or abstract. For instance, I used several synonyms for the exposure (e.g., "cities", "urban

areas", "neighborhoods"), the related social factors (e.g., "social cohesion", "social harmony",

"social unity", "social agreement"), and the outcome (e.g., "schizophrenia" "psychotic disorders",

"severe mental illness") of interest. The proposed keywords were combined for a more precise

search and used to identify titles, abstracts, and full texts in the aforementioned databases (see

Table 1). I searched for articles published from January 2000 to March 2023.

Table 1. Examples of searched keywords per construct.

Urbanicity	"urbanicity" OR "city" OR "urban area" OR "neighborhood" OR "neighborhood" OR "population density" OR "urban/rural" OR "central city" OR " town" OR "ghetto" OR "semirural" OR "rural"
Psychosis	"psychosis" OR "schizophrenia" OR "psychotic disorder" OR "severe mental illness" OR "first

	episode psychosis" OR "FEP" OR "affective psychosis" OR "psychotic symptoms"
Community-level social factors	"social factor" OR "poverty" OR "material deprivation" OR "material constraints" OR "material hardship" "material deficiencies" OR "material problems" OR "marginalization" OR "social disorganization" OR "social dislocation" OR "social disintegration" OR "social disruption" OR "social fragmentation" OR "social ills" OR "social unrest" OR "social upheaval" OR "social inequity" OR "violence" OR "social capital" OR "social cohesion" OR "social harmony" OR "social unity" OR "social agreement" OR "harmonious society" OR "social coherence"

Identified papers were imported into Covidence (https://www.covidence.org) and duplicates removed. Articles published in international peer-reviewed journals, including conference papers, book chapters, and editorial materials, were included in this review if they (a) examined the urbanicity-psychosis association in any country; (b) offered specific, conceptual, and operationalized definitions for urbanicity and related factors; and (c) were written in English, Spanish, and/or Portuguese. I considered a definition to be conceptual if it specified what needs to be assessed in empirical evidence. Additional articles were identified by reviewing the reference sections of the articles found in the literature search. Citation tracking through Google Scholar was also done.

Following the PRISMA guidelines, each report was reviewed sequentially (searching, refining search strategy, examining titles and abstracts, and reviewing full articles). First, titles and abstracts were screened to exclude records that were not relevant. Furthermore, records that were only short commentaries, conference abstracts, book reviews, and letters to editors were also excluded. For all records selected during initial screening, full-text articles were retrieved and assessed to check whether they fulfilled the inclusion criteria (e.g., included a conceptual definition of urbanicity in the full text). I conducted no further assessment of the validity or quality of the full texts as the aim was to identify a broad range of conceptual definitions used in the literature on urbanicity in psychosis research. Considering the lack of a

consensual definition of urbanicity described earlier, I felt it would be arbitrary and possibly counter-productive to rate a priori the quality of some definitions higher than others.
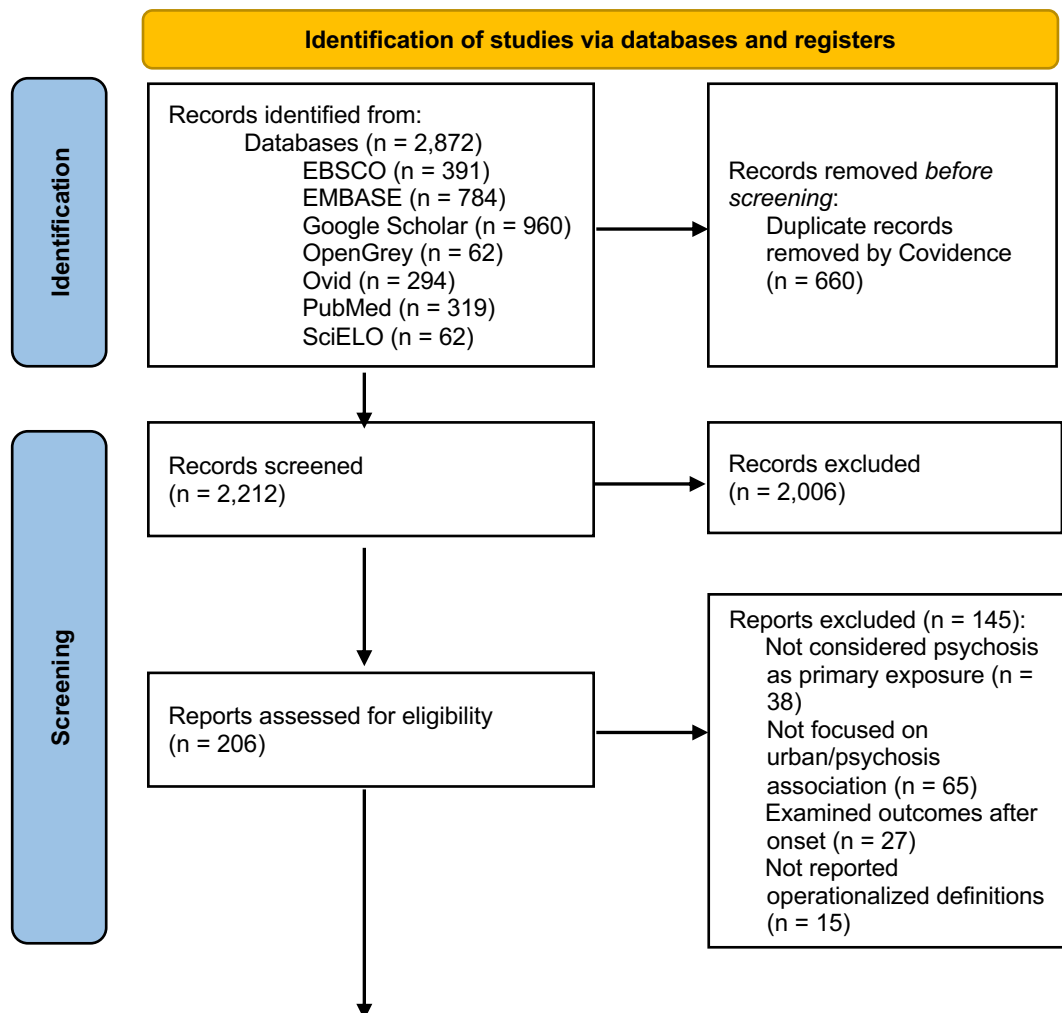
Data analysis and synthesis

I used a thematic analytic approach to organize and synthesize definitions of urbanicity and related factors in psychosis research. My approach was informed and validated by the principles of the grounded theory for qualitative research, as well as previous QSLRs (Butler et al., 2016; Hamid, Ghaleb, Aljadhey, & Aslanpour, 2014; Mansfield, Patalay, & Humphrey, 2020; Salm, Ali, Minihane, & Conrad, 2021). Four full texts were randomly selected, and the included definitions were initially coded to develop a preliminary coding sheet. The following data were extracted from each of the full texts: 1) author and publication year; 2) country or countries where the study occurred; 3) study design, study goals, and sample sizes; 4) which types of psychosis (e.g., non-affective psychosis) the study focused on; 5) definition(s) for urbanicity (and semirural and rural) and related factors; 6) data collection method; and 7) main findings. Moreover, for articles that contained more than one definition or description of urbanicity, all the definitions were included and organized line-by-line under the author   .
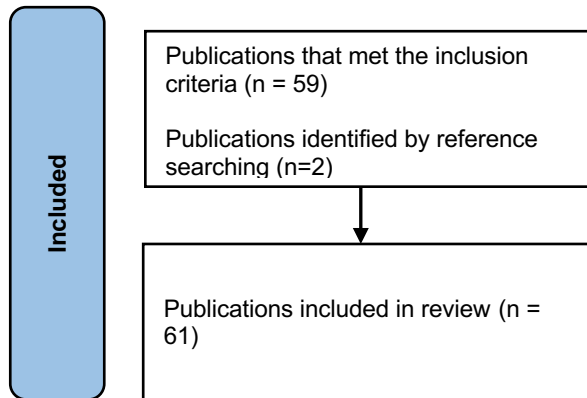
My approach for coding data entailed the following steps: 1) Initial coding (i.e., create categories based on reading definitions from four randomly selected publications); 2) Focused coding (i.e., use categories to organize definitions inductively based on thematic similarity and shared principles); and 3) Theoretical coding (i.e., integrate categories into broader constructs and level of analysis). For each paper, I identified each definition and divided it into meaningful units that we subsequently coded. Then, I coded the definitions in the remaining full texts while continuously extending the coding sheet if new codes emerged while analysis of new full texts. Finally, I grouped them into meaningful clusters based on prior research (e.g., aggregated them into different dimensions of urbanicity).

Results

      A systematic search yielded 2,872 records; I excluded 660 duplicates. I screened 2,212

abstracts, of which 2,006 were excluded, yielding 206 full articles to be included in this review.

Of these articles, 145 were excluded, mainly because they did not 1) consider urbanicity as the

primary exposure or one of the primary exposures (i.e., urbanicity was included as a potential

confounder in the analysis), 2) examine the onset of psychosis as a primary outcome but rather

outcomes that occur after the onset (e.g., treatment adherence, mortality, comorbidity), and 3)

report operationalized definitions for urbanicity (e.g., literature reviews and viewpoints). Two

papers identified by reference searching were included. Finally, 61 articles met the selection

criteria. A PRISMA flow diagram of the selection process can be found below.

Figure 1. PRISMA flowchart for QSLR

Publications that met the inclusion criteria (n = 59)

Publications identified by reference searching (n=2)

Publications included in review (n = 61)

Characteristics of the studies

In this review, I analyzed a variety of reports, with the majority being extensive studies conducted in the Global North (which refers mostly to Australia, North America, and Western Europe) (Allardyce et al., 2005; Bartlett et al., 2007; Bosqui et al., 2022; Kirkbride et al., 2017; Kirkbride, Jones, Ullrich, & Coid, 2014; Kirkbride et al., 2007; Lee et al., 2020; Newbury et al., 2016, Newbury et al., 2018; Newbury et al., 2019; Newbury et al., 2022), including the UK, Denmark (n=11) (Cantor-Graae & Pedersen, 2007; Engemann et al., 2020; Paksarian et al., 2018; Pedersen & Mortensen, 2001; Pedersen & Mortensen, 2006a; Pedersen & Mortensen, 2006b; Schofield et al., 2017; Sørensen et al., 2014; Torrey, Mortensen, Pedersen, Wohlfahrt, & Melbye, 2001; van Os, Pedersen, & Mortensen, 2004; Vassos, Agerbo, Mors, & Pedersen, 2016), Germany (n=5) (Guloksuz et al., 2015; Haddad et al., 2015; Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2004, 2006; Stepniak et al., 2014), Sweden (n=4) (Harrison et al., 2003; Sariaslan et al., 2015; Sundquist, Frank, & Sundquist, 2004; Zammit et al., 2010), the Netherlands (n=4) (Dragt et al., 2011; Kaymaz et al., 2006; Radhakrishnan et al., 2019; van Os, Hanssen, de Graaf, & Vollebergh, 2002), Australia (n=3) (Colodro-Conde et al., 2018; Eaton et al., 2019; McGrath et al., 2001), Greece (n=2) (Mimarakis, Roumeliotaki, Roussos, Giakoumaki, & Bitsios, 2018; Stefanis et al., 2004), the US (n=2) (Karcher, Schiffman, & Barch, 2021; Saxena & Dodell-Feder, 2022), and France (n=1) (Szöke et al., 2014). More recent studies have reported data from regions in the Global South, such as China (n=3) (Luo et al., 2019; Wang et

al., 2019; Yang et al., 2015), Brazil (n=1) (Del-Ben et al., 2019), Chile (n=1) (González-Valderrama et al., 2022), India (n=1) (Khare et al., 2020), Indonesia (n=1) (Jaya & Wulandari, 2018), Romania (n=1) (Budisteanu et al., 2020), Taiwan (n=1) (Chang et al., 2019), Turkey (n=2) (Binbay et al., 2012; Ergül et al., 2022), and Uganda (n=1) (Lundberg, Cantor-Graae, Rukundo, Ashaba, & Ostergren, 2009). I found a few initiatives collecting and/or analyzing data from multiple countries (DeVylder et al., 2018; Gayer-Anderson et al., 2020; Plana-Ripoll, Di Prinzio, McGrath, Mortensen, & Morgan, 2021; Roberts et al., 2023; Smeets, Lataster, Viechtbauer, Delespaul, & G.R.O.U.P, 2015; van der Leeuw et al., 2020), three of which included data from countries in the Global South (DeVylder et al., 2018; Gayer-Anderson et al., 2020; Roberts et al., 2023). Most studies in the Global North were based on national and/or regional health registries with clear definitions for urbanicity and well-defined samples. In contrast, several studies in the Global South did not use representative samples, only had cross-sectional assessments, and did not comprehensively characterize the exposure (e.g., only measuring urbanicity at admission) and/or the outcome (e.g., relying on simple self-report questions about having or not having a "psychotic disorder". However, recent, well-designed cohort (Ergül et al., 2022) and case-control (Roberts et al., 2023) studies have reported preliminary results on the association between urbanicity and psychosis in the Global South. The geographical and methodological characteristics of the included studies are summarized below.

Table 2. Summary of characteristics of retrieved publications.

Author & Year	Country/Region	Study Design (1=cohort, 2=case-control, 3=cross-sectional)	Data collection (1=registry; 2=survey, 3=other)	Data collection (other)
Allardyce 2005	U.K.	3	1	
Barlett 2007	U.K.	3	3	medical record
Binbay 2012	Turkey	3	2	
Bosqui 2022	U.K.	3	2	
Budisteanu 2020	Romania	3	3	medical records
Cantor-Graae 2007	Denmark	1	1	

Chang 2019	Taiwan	1	1	
Colodro-Conde 2018	Australia	3	3	data collected from population genotype study
Del-Ben 2019	Brazil	2	2	
DeVylder 2018	World Health Survey (42 countries)	3	2	
Dragt 2011	Netherlands	1	2	
Eaton 2019	Australia	1	3	medical records/ clinic files
Engemann 2020	Denmark	1	1	
Ergül 2022	Turkey	1	2	
Gayer-Anderson 2020	6 countries (U.K., Netherlands, France, Spain, Italy, Brazil)	2	2	
Gonzalez-Valderrama 2022	Chile	3	1	
Guloksuz 2015	Germany	1	1	
Haddad 2015	Germany	3	3	MRI imaging data;
Harrison 2003	Sweden	1	1	
Jaya 2018	Indonesia	3	2	
Karcher 2021	United States	3	2	
Kaymaz 2006	Netherlands	1	2	
Khare 2020	India	3	2	
Kirkbride 2007	U.K.	1	2	
Kirkbride 2014	U.K.	3	3	health service record data
Kirkbride 2017	U.K.	3	3	medical records
Lee 2020	U.K.	1	3	medical records at hospitals
Lundberg 2009	Uganda	3	2	
Luo 2019	China	3	2	
McGrath 2001	Australia	2	2	
Mimarakis 2018	Greece	3	2	
Newbury 2016	U.K.	1	2	
Newbury 2018	U.K.	1	2	
Newbury 2019	U.K.	1	2	
Newbury 2022	U.K.	1	2	
Paksarian 2018	Denmark	2	1	
Pedersen 2003	Denmark	1	1	
Pedersen 2006a	Denmark	1	1	
Pedersen 2006b	Denmark	1	1	
Plana-Ripoll 2021	Denmark, Australia	1	1	
Radhakrishnan 2019	Netherlands	3	2	
Roberts 2023	India, Nigeria, Trinidad	2	2	
Sariasian 2015	Sweden	1	1	

Saxena 2022	United States	1	2	
Schofield 2017	Denmark	1	1	
Smeets 2015	Netherlands, Belgium	3	2	
Sorensen 2014	Denmark	1	1	
Spauwen 2004	Germany	3	2	
Spauwen 2006	Germany	1	2	
Stefanis 2004	Greece	3	2	
Stepniak 2014	Germany	3	3	medical records, comprehensive examinations;
Sundquist 2004	Sweden	1	1	
Szoke 2014	France	1	3	data collected by psychiatrists treating the new cases
Torrey 2001	Denmark	3	1	
van der Leeuw 2020	Netherlands, Belgium	2	2	
van Os 2002	Netherlands	3	2	
Van Os 2004	Denmark	3	1	
Vassos 2016	Denmark	1	1	
Wang 2019	China	3	2	
Yang 2015	China	3	2	
Zammit 2010	Sweden	1	1	

Thematic analysis

The coding process was developed based on a data-driven approach. Extracting information based on each article's definition, measurements, and categorizations of urbanicity for each article, I was able to reduce it to a set of themes and categories (see Table 3). Of note, more than one of these categories could be used in a study.

In summary, the most common category used to define urbanicity was "population density," accounting for 67.74% of the papers included (n=42). Followed by the codes "granularity/categorization of urbanicity" (n=34) and "administrative divisions" (n=30), which were utilized in 54.84% and 48.39% of the papers, respectively. Furthermore, codes pertaining to themes related to neighborhood-level mechanisms were used the least often. We found that "walkability" was used in of the papers, followed by "social deprivation" (n=4), "social fragmentation" (n=3), and social capital (n=1).

Through my data analytic approach, I identified a series of codes, presented in Table 3. These codes were aggregated into three thematic categories that reflect the contents and scope of the definitions of urbanicity, and how they have been used when studying the association between urbanicity and psychosis. These categories include: (a) Urbanicity involves several interconnected constructs, (b) Urbanicity measurement varies across studies and regions, and (c) Urbanicity operates through some key neighborhood-level mechanisms.

Table 3. Definitions and examples of urbanicity and community-level social factors.

	Category/code	Definition	Example
A	**Interconnected constructs**		
A1	Population density	Population density is the number of individuals per unit geographic area (e.g., number per square meter, per hectare, or per square kilometer).	**Gonzalez-Valderrama et al. (2020)**: Urbanicity was based on population density. Expressed in number of residents per squared kilometer and number of resident per squared hectare.
A2	Total population	Total number of individuals in the census or national registry.	**McGrath et al. (2001):** degree of urbanization was divided into three categories according to population at time of birth ("city" ≥100,000, "town" > 10,000 and < 100,000,"rural" ≤10,000).
A3	Granularity/categorization of urbanicity	Level of detail in the categories used for urbanicity classifications and data analysis (e.g., binary measure, 5-level categories)	**Bosqui et al. (2020)**: Urban-rural classifications, referred to herein as 'urbanicity', was calculated based on 8 settlement bandings, ranging from the most urban area (with a population of 75,000 or over) to the most rural (less than 1,000 people)
A4	Administrative divisions	Defined urbanicity directly by pre-determined administrative division of areas (e.g., neighborhoods, provinces, regions)	**Vassos et al. (2016):** Municipalities in Denmark were classified according to degree of urbanization as follows: capital, capital suburb, provincial cities, provincial towns or rural areas.
B	**Urbanicity Measurement Global North versus Global South**		
B1	Social and Educational indicators	Composite measures composed of several indicators on urbanicity included but not limited to demographic, social, and economic indicators	**Chang et al. (2019):** Several indicators including population density (people/km2), population ratio of people with college or above educational levels, population ratio of elder people over 65 years old, population ratio of people of agriculture workers and the number of physicians per 100,000 people and used the cluster analysis with squared Euclidean distance and Wald's minimum variance method, to study the urbanization stratification of varied township in Taiwan. **Tessa et al. (2023):** Urbanicity in India was defined as minimum population of 5000; at least 75% of the male main workers engaged in non-agricultural pursuits; and population density of at least 400 per sq. km'
B2	Geographical unit	Urbanicity measured for unit of area (e.g., districts, cities, provinces)	**Allardyce et al. (2005):** The degree of urbanicity is calculated for each postcode sector by adding to the population total the population of each directly adjacent neighborhood: category 1 is most urban, and category 5 and 6 are the most rural.
B3	Timing	When urbanicity is measured (e.g., at birth, upbringing, at first contact)	**Newbury et al. (2020):** Urbanicity was derived from classifications from 2011 census data (Office for National Statistics, 2013) and linked to participants' home postcodes at ages 5, 12, and 18.
C	**Community-level social mechanisms**		
C1	Ethnic density	Suggests that the risk of psychosis increases for ethnic minority groups as they live in communities with fewer members of their own ethnic group	**Kirkbride et al. (2014):** We used the 2001 census to estimate population density (people per hectare), own-group ethnic density, own-group ethnic separation, and social fragmentation. We defined own-group ethnic density in each statistical ward as the size of one's own ethnic group as a proportion of total neighborhood population.

C2	Social fragmentation	Absence or underdevelopment of connections between individuals and society in a particular geographic area	**Zammit et al. (2010):** Municipality-level data included measures of urbanicity (city [Stockholm, Gothenburg, and Malmo], town [20 000 inhabitants in 1980], rural [20 000 inhabitants]), population density, and markers of deprivation (derived by summing z scores for mean income, proportion unemployed, and proportion receiving welfare benefits) and social fragmentation (derived by summing z scores for proportion of people migrating in/out of the municipality, voting in municipality elections, individuals married, and single-person households).
C3	Social Deprivation	Limited access to society's resources due to poverty, discrimination, or other disadvantage	**Lee et al. (2020):** We adopted the Welsh Index of Multiple Deprivation (WIMD) 2011 as a measure of area deprivation at lower-layer super-output area (LSOA) level, the geographic units used in the calculation of WIMD and the reporting of small area statistics comprised of approximately 1500 individuals (Welsh Government, 2017). Eight different domains of deprivation were assessed, namely, income, housing, employment, geographical access to services, education, health, community safety and physical environment.
C4	Social capital	How social relations and networks influence collective action for mutual benefit	**Ergül et al. (2022):** Four dimensions of neighborhood-level social capital were assessed: informal social control, social cohesion and trust, social disorganization, and cognitive social capital. The informal social control scale included eight questions measuring the willingness to intervene in hypothetical neighborhood-threatening situations such as children misbehaving, using a five-point Likert scale ranging from 'strongly disagree' to 'strongly agree'. The social cohesion and trust scale measured bonds and trust among neighborhood residents. The social disorganization scale consisted of eight questions rating the frequency of certain scenarios occurring in the participant's neighborhood, such as the presence of graffiti, vandalism, burglary and racist attacks. The cognitive social capital scale included three questions measuring perceptions of support, reciprocity and sharing among the residents of the neighborhood. For each social capital dimension, sum scores were (negative items were reversed) divided by the number of items and aggregated to the neighborhood level.
C5	Walkability and Perception of neighborhood safety	A walkable place is a place easy to walk around based on three indicators: design, distance, and diversity. Parents' views of neighborhood safety based on exposure to crime and violence.	**Karcher et al. (2021):** A neighborhood walkability index was created based on data obtained from EPA. **Karcher et al. (2021):** Perception of Neighborhood safety was calculated as a summation of 3 parent-rated questions (ie, "I feel safe walking in my neighborhood, day or night"; "Violence is not a problem in my neighborhood"; "My neighborhood is safe from crime"); each was rated on a scale from 1 to 5 (1¼strongly disagree, 5¼ strongly agree).

Urbanicity involves several and interrelated constructs.

As expected, there is not a single, coherent definition of urban versus rural in the psychosis research literature. Most studies used "population density" as a proxy for defining and assessing urbanicity. However, there was substantial variation in how this construct was operationalized in terms of what constituted an "individual" (e.g., residents at a time point, incident vs prevalent, current urbanicity versus birth/childhood urbanicity), a "unit" (e.g., per hectare), or a "geographical area" (e.g., region).

Moreover, researchers have used other constructs such as total urban and rural population (i.e., the total number of individuals in the census or national registry) (Radhakrishnan et al., 2019), administrative divisions (i.e., previously determined codes of urban/rural, that is administrative areas that have been previously defined as urban/rural) (Vassos et al., 2016), and multidimensional criteria to distinguish urban from rural or semirural areas (e.g., dimensions such as hectare grid squared postcodes, and settlement polygons) (Lee et al., 2020). Others have noted that urban areas usually entails a series of conditions such as overcrowding, environmental pollution, and violence compared to rural areas (Chang et al., 2019). Other characteristics of urbanicity can include people involved in non-agricultural activities ("at least 75% of the main male workers engaged in non-agricultural pursuits") (Roberts et al., 2023), remoteness ("distance from main cities or difficult access") (Roberts et al., 2023), and hectare grid squares, postcodes, and settlement polygons (Allardyce et al., 2005).

These measures have different meanings, depending upon what constitutes the geographical region of interest. As noted by Kirkbride et al. (2018) a broad geographical area often contains a mixture of many different social conditions, making it difficult to characterize it as entirely urban or rural under any concept. Small areas may be more socially uniform, but small area characteristics also may not be the appropriate level to measure the concept, for

example, if the concept is living within a sizeable dense metropolis. These constructs are often interrelated (e.g., population density is used to construct geographical categories or units).

Urbanicity measurements vary between countries from the Global North and the Global South

Urbanicity measurement varies significantly across studies and regions in psychosis research. Most studies in the Global North, especially in Northern Europe (Newbury et al., 2022; Pedersen & Mortensen, 2006a; Sørensen et al., 2014), have used population density as the main proxy for urbanicity based on national census or registries and have detected a strong association between urbanicity (at birth or upbringing) and psychosis onset (Pedersen & Mortensen, 2001; Pedersen & Mortensen, 2006a). In contrast, definitions from some studies in the Global South were somewhat more complex and comprehensive involving level of urbanization (e.g., urban areas versus semirural and rural areas) (Budisteanu et al., 2020) and local geographical classifications (e.g., village, district, province, metropolitan area) (Ergül et al., 2022), as well as social (e.g., agriculture versus non-agricultural jobs) (Ergül et al., 2022) and educational (e.g., population ratio of people with college or above educational levels) (Chang et al., 2019) indicators. More recently, however, several studies from the Global South have also used population density as a proxy for urbanicity (Del-Ben et al., 2019; González-Valderrama et al., 2022). Table 3 provides further details on the different operationalizations for population density and other indicators for urbanicity.

This variation is partly due to the complex and multifaceted nature of urban environments across countries and regions, which makes it challenging to capture all relevant aspects of urbanicity in a single, standard measure. Some measures may be more relevant in different regions or populations. As shown in the selected studies, measures based on population density may be more relevant in highly urbanized countries with advanced infrastructure (e.g., in transportation) (e.g., Global North), while measures based on administrative divisions may be more relevant in regions with many people living in urban and

even mega-urban areas as well as many people living in dispersed villages and in "mixed" regions. In the Global South, there are often no data available except for entities such as administrative regions and these are not uniform with respect to urbanicity. As noted in Table 3, most pre-defined administrative divisions are derived from population density and size measures.

Moreover, these different operationalizations of urbanicity may explain why the consistent results from Northern Europe have not been replicated in other countries in the Global North (e.g., Italy, Spain) (Roberts et al., 2023) and in several countries in the Global South (Gayer-Anderson et al., 2020). Kirkbride et al. (2018) have noted that these results may represent true differences in the meanings and effects of urban and contextual factors (e.g., although "population density" is a standard measure for urbanicity, the nature of living in urban areas may have different meanings for psychosis research). More research in the Global South (and other uncharacterized regions and populations in the Global North) is needed to understand further the particularities and implications of urbanicity compared to semirural and rural areas. Future research should consider local understandings and administrative data, as suggested below.

Urbanicity operates through community-level social mechanisms.

Several studies included in this review suggest that community-level social factors may be potential causal mechanisms for the association between urbanicity and psychosis, such as ethnic density (Schofield et al., 2017), social fragmentation (Zammit et al., 2010), social capital (Ergül et al., 2022), walkability, and neighborhood safety (Karcher et al., 2021). However, these data are still emerging and have not been consistent across countries (even in Northern Europe). There is also variation in terms of how these concepts have been measured. For example, Allardyce et al. (2005) reported that individuals living in the most socially deprived areas were at higher risk of developing psychosis compared to those in less affluent areas. In

this study, social deprivation was assessed using census data on overcrowding, male unemployment, low social class, and not having a car. However, a large Swedish family- and register-based study could not detect an association between population density at first diagnosis (e.g., natural log of the absolute population size per square kilometer) and neighborhood deprivation (i.e., proportion of individuals with less than secondary school qualifications, proportion not married, proportion not born in the Nordic countries, and neighborhood crime rate) with schizophrenia (Sariaslan et al., 2015).

In terms of social cohesion/fragmentation, Zammit et al. (2010) in a register-based study in Sweden (n=203,829), found that the association between living in a city and psychosis was primarily explained by school-level measures, as a proxy for neighborhood social fragmentation (i.e., proportion of children who migrated into Sweden, moved into a different municipality between ages 8 and 16 years, or were raised in single-parent households). The effect of social fragmentation persisted even after controlling for individual-level confounding factors, such as age and foreign-born status. Furthermore, Kirkbride et al. (2014) identified a non-linear association between levels of social cohesion/fragmentation in neighborhoods (e.g., indicators on the presence of graffiti, teenagers, vandalism, attacks due to race or skin color, other attacks, burglary, and theft of or from vehicles in a particular neighborhood) and schizophrenia incidence.

In the Global South, these factors are yet to be fully characterized and examined. Urbanicity in some countries, in both Global North and South, may have positive effects. For example, the availability of health and social resources in cities versus rural areas may moderate (i.e., mitigate) the negative urbanicity effects (Kirkbride et al., 2018). Some studies have used complex yet locally sensitive operationalizations. For instance, González-Valderrama et al. (2022) measured poverty using a multidimensional index from the Chilean Biennial National Socioeconomic Characterization Survey, which has been administered for over two decades, including indicators such as childhood malnutrition, lack of health insurance, the deficit

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in healthcare, school attendance, low level of education, school delay, lack of employment, lack of social security, lack of retirement benefits, overcrowding, poor structural housing quality, and deficit in essential services.

Discussion

      In this review, I examined how urbanicity has been defined in the psychosis research literature. There was not a single, coherent definition of urban versus rural/semirural areas across studies and regions. The main findings of the review are discussed below.

      Urbanicity is a multifaceted construct, including not just population density and geographical units, but also encompassing various capabilities such as education opportunities, access to cultural resources, and social engagements. Instead of a monolithic definition based on numbers of people in a particular geographical area, urbanicity should be understood as a dynamic space where individuals' capabilities can be nurtured or restrained. The Capability Approach emphasizes the importance of the opportunities available to individuals that allow them to live the lives they value (Sen, 1985, 1999), which is critical when considering how urban environments can increase the risk of mental health conditions. To truly capture this dynamic, researchers should consider a multidimensional approach to operationalize urbanicity, one that is informed by local conceptualizations of valued capabilities and resources, rather than relying on a singular, standardized measure such as population density. As noted by Susser (2021), the study of urban requires an analysis of historical and contextual factors, such as economy, migration, and politics, rather than focusing exclusively on the number of individuals in a particular area (e.g., literature on precarity).

      Several studies in the Global South used comprehensive, locally sensitive measures in addition to more standard constructs such as population density. This finding is promising as in some instances rural areas may have higher levels of population density than parts of urban areas in the Global South, which can complicate the use of population density as a measure of

urbanicity. However, as noted previously, this finding is subjected to the way urbanicity is defined and operationalized. Similarly, in some regions, administrative divisions may not accurately capture urban environments' social and cultural dynamics. Therefore, it is important for researchers to consider the operationalization of urbanicity in their studies carefully and to select appropriate measures for the population and region being studied as well as the questions being examined. This may involve developing context-specific measures of urbanicity that consider the unique characteristics of different urban and rural/semirural environments (including potential moderators such as access to healthcare and other social services). The INTREPID II study was full of challenges, but it serves as a good example of using meaningfully informed definitions for urbanicity. The researchers utilized different, locally validated measures for urbanicity when comparing Trinidad, India, and Nigeria (Roberts et al., 2023).

Moreover, most studies in this review did not thoroughly characterize the comparison group/area (i.e., rural or semirural areas). There has been a great interest in characterizing urban living, but much less is known about the effects of being born and growing up in rural or semirural areas, ignoring the capabilities these areas might offer or lack. There is a dearth of psychosis research in rural areas in both the Global North and the Global South (Peritogiannis & Samakouri, 2021). This is problematic for psychosis research in both regions but for different reasons. In the Global North, rural areas have been transformed into semirural areas in most countries recently, which has changed the living conditions of residents at several levels. The effects of such changes are yet to be understood, but they may modify the direction and strength of the urbanicity/psychosis association. In the Global South, although the level of urbanization has increased dramatically over the years, there are still many people who live in rural areas and who experience disadvantageous conditions, such as social deprivation and social fragmentation, which are typically found in urban areas in the Global North. Therefore, the varied definitions of urban versus rural across different regions and the transformation of many

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rural areas into semi-rural spaces, suggest the need to delve deeper into how these environments nurture or diminish capabilities, potentially increasing psychosis risk.

There is emerging research identifying and describing the moderation effects of some community-level social factors (e.g., social deprivation, social capital) between urbanicity and psychosis. As with urbanicity, the definitions for these factors also vary substantially across studies. There is not a comprehensive, multidimensional approach for measuring and testing the mediational effects and the association between factors, as many could be both mediators and moderators of the urbanicity-psychosis association depending on the research question. Additionally, the characterization of these factors in the Global South is very limited.

Future research on psychosis and urbanicity should aim to address some of the current limitations of the existing literature. We focus on the Global South as many of these gaps have been reported there, although some often apply to the Global North as well. Potential avenues of research include:

1. <u>Greater attention to historic and contextual factors</u>: Given the vast cultural, economic, and social differences between the Global South and Global North, and within the Global South, future studies should address contextual factors that may influence the relationship between urbanicity and psychosis. This could include factors such as social norms; local and cultural practices; social, health, and economic inequities; new waves of migration from rural to urban areas within and between countries (e.g., South to South migration) (Ratha & Shaw, 2007); and rapid environment changes due to climate conditions, armed conflict, and social and civil unrest. Moreover, we should consider the colonial legacy of drawing arbitrary boundaries between countries that comprise populations without a shared history and culture, or creating divisions along these lines that did not exist before. These factors are often the roots of civil unrest now, and they occur in both urban and rural areas but in different ways.

2. <u>Use of locally derived measures</u>: To facilitate relevant research on urbanicity and psychosis onset in a particular context, as well as meaningful comparisons across different regions and populations, future studies should use locally informed measures to define and operationalize the exposure and document how these measures align or differ from standard definitions. This could involve the development of region-specific measures that consider local variations in urbanization patterns, change in living conditions over time, and transformation of the healthcare system (and other services).

3. <u>Focus on the multifaceted aspects of urbanicity</u>: As it has become clear, urbanicity involves a series of contextual, social, and political factors shaping individuals' experiences and limiting (or enhancing) human capabilities. Future studies should examine these factors in detail, in particular, their association with mental health well-being and psychosis risk in urban areas. Factors of special relevance include social cohesion, social fragmentation, neighborhood disorder, and religious and cultural traditions. This could involve the use of innovative methods such as spatial analysis and social network analysis.

4. <u>Mixed-methods approaches</u>: Given the complex and multidimensional nature of urbanicity and psychosis, future research should employ mixed-methods approaches that combine quantitative and qualitative data collection methods. This could involve the use of surveys, interviews, and observational methods to provide a more comprehensive understanding of the relationship between urbanicity and psychosis. Research on architecture and urbanism (Winz, 2018) and urban anthropology (Susser, 2021), using ethnographic techniques, can shed light on what it means to reside, interact, and navigate current urban versus rural/semirural areas.

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Urbanicity and psychosis: a Chilean registry-based cohort study

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Abstract

Background: We examined the association between urbanicity at birth and nonaffective first-episode psychosis (FEP) using a registry-based study population from Chile. Although urban areas might offer opportunities for human development (access to services), they might also present overwhelming challenges (e.g., overcrowding), impacting individuals' capabilities and mental well-being. The urbanicity-psychosis association has been extensively studied in the Global North, but research from the Global South has yielded mixed and inconsistent results. Methodological limitations can explain some of these results. Rigorous research programs using nationwide registries from the Global South are warranted.

Methods: We created a cohort (year of birth: 1992-2012) using the Chilean Civil Registration and FEP registries. The study population comprised 5,137,561 individuals. Of those, we identified 14,410 with confirmed nonaffective FEP between 2005-2022. The hypothesized association considered the exposure of interest (urbanicity at birth), the outcome of interest (FEP), and potential confounders (year of birth, region). We first calculated crude incidence rates of having confirmed nonaffective FEP diagnosis per 100 000 person-years. We then used Poisson regression to estimate incidence rate ratios (IRR) and control for confounders (Model 1: year of birth; Model 2: year of birth, region). We also conducted additional analyses to explore whether urbanicity had a differential effect on psychosis among males versus females.

Results: Over a total of 91.96 million person-years, we observed a crude incidence rate of 15.67 cases per 100,000 person-years (95% confidence interval [CI]: 15.42-15.93). The unadjusted model revealed a null association between urbanicity at birth and risk of nonaffective FEP in Chile (IRR: 0.97; 95%CI: 0.92 – 1.02). Adjusted models 1 (IRR: 1.06; 95%CI: 1.01 – 1.11) and 2 (IRR: 0.96; 95%CI: 0.91 – 1.01) yielded similar null results. We found a small association between being born in an urban area and psychosis among males, and a nonsignificant trend among females.

Discussion: Our findings do not align with previous research conducted in the Global North, especially Northern Europe. However, they do contribute to the emerging evidence indicating that the urbanicity/psychosis association may not pertain to the Global South. This study represents the most rigorous and comprehensive effort to estimate the effect of urbanicity on psychosis ever done in the Global South.

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Background

Studies reporting increased rates of mental disorders in urban areas have a long history in psychiatric epidemiology. One example is the set of landmark studies by Faris and Dunham in Chicago in the late 30s who found that most cases of schizophrenia were in the most populated and socially deprived areas of the city (i.e., "Centre city") (Faris & Dunham, 1939). In 1992, Lewis et al. conducted a national, registry-based study aimed to examine the association between place of upbringing and the incidence of schizophrenia, using data from a cohort of male conscripts (n=49,191) in Sweden (Lewis et al., 1992). The incidence of schizophrenia among men who were brought up in cities was 1.65 times the rate in men who had had a rural upbringing, after controlling for individual-level confounders including use of cannabis, parental divorce, and family history of psychiatric disorders (Lewis et al., 1992).

In the early nineties, Marcelis et al. using population registries from the Netherlands found that individuals with urban birth and/or urban exposure at adolescence were at higher risk of developing schizophrenia after controlling for birth cohort, season of birth, and age of onset (Marcelis et al., 1998; Marcelis et al., 1999). These results supported the hypothesis that being born in an urban environment increases the risk of schizophrenia. Mortensen et al. (1999), in a large sample of 1,750,000 individuals from Denmark (N= 2,699 with schizophrenia), reported that those born in Copenhagen were at the highest risk of presenting schizophrenia compared to individuals from rural areas, with a gradient in risk by degree of urbanization of birthplace. Moreover, a series of studies reported a linear dose-response association between the risk of developing schizophrenia and the number of years spent in a highly urban environment before age 15 in Denmark (e.g., living in an urban area at age 5 and at birth was associated with increased psychosis risk compared to have lived always in rural areas) (Pedersen & Mortensen, 2001, 2004; Pedersen, 2006).

These consistent results from Northern Europe have not been replicated in other countries in the Global North, such as Italy and Spain (Jongsma et al., 2018), and in the Global

South, such as Brazil (Del-Ben et al., 2020), China (Phillips et al., 2009), and Chile (González-Valderrama et al., 2020). For instance, a large multicenter study did not detect an association between urbanicity and incidence of psychosis in several European countries (Jongsma et al., 2018). Analyses by country, however, revealed significant associations between urbanicity and psychosis in the UK and the Netherlands, but not in Italy and Spain (Jongsma et al., 2018). These differences between Northern European countries and Southern European countries are yet to be explained. One possible explanation is that these results represent true differences in the meanings and effects of urban and contextual factors on psychosis. For instance, although "population density" is a common measure for urbanicity, the nature of living in urban areas may have different effects on individuals in Southern Europe compared to Northern Europe on psychosis, as well as disease distribution and etiologic mechanisms. These differences could also explain the mixed results reported in the Global South.

Little research on the urbanicity-psychosis association has been done in the Global South. Additionally, most evidence come from prevalence studies, limiting causal inference and comparisons with incidence studies from Northern Europe. That said, the studies conducted to date have yielded mixed results. For instance, in an especially rigorous two-stage prevalence study in four provinces in China (Phillips et al., 2009), there were no differences in the odds of detecting psychotic disorders when comparing individuals from urban vs rural areas. Similar results from less rigorous studies have been reported in India (Ganguli, 2000) and Tibet (Wei et al., 2008). Although other studies have found evidence supporting the causal link between urbanicity and psychosis in China (Xiang et al., 2008) and Uganda (Lundberg, 2008), recent evidence from China (Long et al., 2014), Sao Paulo, Brazil (Del-Ben, 2020), and Chile (González-Valderrama et al., 2020) indicates that the urbanicity-psychosis association may not pertain to settings outside Northern Europe. For instance, a recent report from Chile did not detect an association between the incidence of non-affective psychosis and regional population density at admission (González-Valderrama et al., 2020). Moreover, a case-control study

conducted in Trinidad and Tobago, Nigeria, and India, found a positive association in some places (e.g., Northern Trinidad) but not in others (e.g., India) (Roberts et al., 2023). These results are intriguing, do not support the consistent evidence coming from Northern Europe, and have implications for future research to be conducted in the Global South.

The Capability Approach, proposed by Amartya Sen, can help us understand these findings. This approach looks at well-being, including mental health well-being, in a broader way, not just by what resources people have or the outcomes they achieve, but by their real opportunities to live fulfilling lives (Brunner, 2017). It focuses on the idea that people need the freedom to live lives that they value (Nussbaum, 2000). When we apply this to the urbanicity/psychosis association, the approach indicates that the experiences of living in an urban area and how it affects what people can do or be can vary a lot from place to place. In the Global North, cities might offer better education, more social activities, and better healthcare, which can help people do more with their lives. However, these opportunities might not be available to everyone, especially immigrants or minority groups who might live in crowded places with few services and a lot of stress, increasing their psychosis risk (Jongsma et al., 2021). On the other hand, in the Global South, urban areas might offer on average more advantages than disadvantages, especially in terms of personal growth and opportunities, which might help explain why some studies have not found a clear link between urbanicity and psychosis.

Furthermore, in explaining these results, we should also keep in mind some methodological considerations. In contrast to research from Northern Europe, most studies from the Global South have only included individuals currently living in an urban environment with no adjustment for exposure time, whether participants were temporary migrants, or if the participants were born in and/or exposed to urban environments during infancy and adolescence. Moreover, causal mechanisms, encompassing social and environmental variables, are largely uncharacterized in the Global South. These could play roles as mediators

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and moderators of the association between urbanicity and psychosis. Data on these variables may help us to better understand the variations between Northern Europe and other countries, and how urbanicity increases or decreases the risk for psychosis in certain countries but not in others. Furthermore, variation on the urbanicity-psychosis association between regions/provinces/cities within countries in the Global South is also expected, as in the Global North, though studies have not usually made such distinctions.

Many studies from Northern Europe have used data from excellent nationwide registries in which most people, if not all, are included. Almost no countries in the Global South have such research structure in place and the quality of the data available from registries is usually low. One exception is Chile. In this country, there are several population-based registries in which everyone is identified by a national identifier obtained at birth (called "RUN", in Spanish). Since 2005, a government legislation mandates that any person who develops non-affective or affective FEP must be recorded on a specific registry for FEP. Cases are ascertained through standard and thorough procedures including clinical interviews conducted by trained psychiatrists and other mental health professionals (Minoletti et al., 2021; Markkula et al., 2011).

As noted previously, González-Valderrama et al. (2018) reported a null association between regional population density (i.e., a proxy for urbanicity) and incidence of nonaffective FEP in Chile using data from the Chilean FEP registry and national censuses. However, they did not measure urbanicity before onset (e.g., at birth or upbringing), differentiate between "suspected" and "confirmed" cases (i.e., confirmation occurs after six months with a third of the suspected cases not being confirmed based on a prior report), include crucial data on potential confounders (e.g., parental antecedents), and use data from a population-based cohort.

We examined the association between urbanicity at birth and the incidence of nonaffective FEP using novel data from a nationwide, cohort (year of birth: 1992-2012) in Chile. We hypothesized that people who were born in urban areas would be at higher risk of developing FEP, but the effect estimates would be of smaller magnitude compared to the results

reported in Northern Europe. We controlled for key confounders such as year of birth and region. We also hypothesized that urbanicity could have a differential effect on psychosis among males versus females. The Chilean registries are unique and comprehensive allowing us to examine the urbanicity/psychosis association thoroughly for the first time in the Global South.

Methods

Study design and data sources

This was a registry-based study using data from two sources: 1) the Chilean FEP registry (2005-2022), and 2) the Birth and Death registry (1990-present).

As noted previously, the Chilean FEP registry includes every individual with "suspected" or "confirmed" FEP since 2005. Clinical staff at every locale in Chile reports the FEPs to the registry and the Ministry of Health updates the registry annually. Around 70-80% of suspected cases are later confirmed (Markkula et al., 2011). The FEP registry includes data on several individual-level variables such as diagnosis (ICD-10 codes from F20 to F29), age, gender, date of admission, place of admission/residence, and socioeconomic status of the parents (e.g., education and employment). The conceptual and administrative structure of this registry has not changed since 2005.

The Birth and Death registry includes all the variables recorded for every birth and death in Chile. This registry includes about 99% of the total population. The Civil Registration manages this data source which includes everyone with a national identifier. For births, the data recorded includes the national ID number for the newborn, their height and weight, and specifics of their birth including its location, the delivery attendant, and the nature of its recording. There are several variables directly concerned with the parents of the newborn, and more directly, their educational attainment, and employment status. It also includes data on the region, province, and commune or "comuna" (i.e., a municipality-level subdivision) where the child lives.

Study population

We created a cohort including every person who was born in Chile between 1992-2012. We identified those with FEP using the Chilean FEP registry. We included all individuals registered with a FEP in Chile between 1 January 2005 and 31 December 2022. We estimated the denominator of person-years based on the full historical cohort and the time range of observation (2005-2022).

Based on the original cohort containing 6,977,202 individuals, participants were excluded if they: 1) were born before 1992 or after 2012 (n = 1,798,973); 2) deceased before 2005 (n = 40,631); and 3) were diagnosed before 2005 (n = 37). We included 5,137,561 individuals in the current study.

Measures

Outcome: The primary outcome for this study was a clinical diagnosis of nonaffective FEP according to the ICD-10 (F20–F29). A national mental health law mandates that a careful diagnostic process led by a psychiatrist take place after a 6-month period. Both suspected and confirmed FEP cases are recorded in the FEP registry. We only used confirmed cases for this report following standard procedures reported previously (Larach et al., 2020).

Exposure: We used a dichotomous urban/rural variable from the National Institute of Statistics which is based on population density, housing, and employment (INE, 2019). This measure represents urbanicity *at birth*. In this conceptualization, an <u>urban area</u> is defined as "a human settlement with continuity and concentration of buildings in a regular block with a population greater than 2,000 inhabitants, or between 1,001 and 2,000 inhabitants, where less than 50% population who declare to have worked are engaged in primary activities (e.g., agriculture, fishing, forestry)." In contrast, a rural area is "a concentrated or dispersed human settlement with 1,000 or fewer inhabitants, or between 1,001 and 2,000 inhabitants, where more than 50% of the population who declare to have worked are engaged in primary sector activities." In this

context, primary sector activities relate to activities whose end purpose is in exploiting natural resources. The National Institute of Statistics have used this variable for decades for both programmatic and research purposes. The conceptualization is locally valid and more nuanced than standard proxies for urbanicity which typically rely only on population density.

Confounders: We controlled for two potential confounders: year of birth and region. We used a standard taxonomy by the National Institute of Statistics to group regions into five large areas: *Northern Area* (Arica y Parinacota, Tarapacá, Antofagasta, Atacama), *Central Area* (Coquimbo, Valparaíso, Metropolitan Santiago), *Central South Area* (O'Higgins, Maule, Ñuble, and Biobío), *Southern Area* (La Araucanía, Los Lagos y Los Ríos), *Southernmost Area* (Aysen y Magallanes, and the Chilean Antarctica). The Central and Central South areas include the most densely populated regions such as Metropolitan Santiago (Capital), Valparaiso, and Bio-Bio. The Northern area includes large arid landscapes and border cities (e.g., Arica) with an increasing migrant population. The Southern and Sourthermost areas have large rural areas and small towns and villages. Agriculture and the forestry industry are important in this area.

I controlled for age and region because there were differences in urbanicity and psychosis rates by year of birth and region (see Table 1). We did not include gender as confounder as there were no differences in urbanicity by gender. Other variables in the data set—such as parental antecedents and health insurance—were not included as confounders. For example, health insurance was more likely an outcome rather than an antecedent of psychosis. Additionally, while parental antecedents differed between individuals with and without psychosis (outcome), they showed no association with urbanicity (exposure). More on parental antecedents in Paper 3, below.

Table 1. Characteristics of the population by urbanicity

Variables	All participants (n = 5137561)		Urban (n = 4552194)		Rural (n = 585560)	
	N / Mean	% / SD	N / Mean	% / SD	N / Mean	% / SD
Sex at birth						
Male	2,623,047	51.06	2,325,555	51.09	297,399	50.79
Female	2,514,365	48.94	2,226,317	48.91	287,948	49.17

Undetermined	149	< 0.01	129	< 0.01	20	< 0.01
Year of birth						
Before 1997	1,582,833	30.81	1,375,666	30.22	207,150	35.38
1998~2002	1,165,424	22.68	1,023,974	22.49	141,274	24.13
2003~2007	1,154,263	22.47	1,036,751	22.77	117,512	20.07
2008~2012	1,235,041	24.04	1,115,610	24.51	119,431	20.40
Region at birth						
Northern Region	454,461	8.85	441,113	9.69	13,328	2.28
Central Region	2,794,980	54.40	2,662,983	58.50	131,913	22.53
Central South Region	1,161,450	22.61	918,313	20.17	243,074	41.51
Southern Region	646,641	12.59	454,942	9.99	191,675	32.73
Southernmost Region	80,029	1.56	74,650	1.64	5377	0.92

Data analysis plan

We processed, cleaned, and prepared the data for analysis keeping the same labels, descriptions, and codes as the original data set. We conducted descriptive analyses for each variable of interest, including exposure, outcome, and potential confounders. We examined continuous variables using arithmetical means and standard deviations. We explored categorical variables using tabular analyses to assess frequencies and proportions. Moreover, bivariate analyses were performed to assess age and gender patterns in each variable of interest.

The primary analysis considered the exposure of interest (urbanicity), the outcome of interest (FEP), and potential confounders (year of birth and region). To examine this association, we first calculated crude incidence rates of having confirmed nonaffective FEP diagnosis per 100 000 person-years (2005-2022) and 95% Confidence Intervals (CIs) by urbanicity, gender, year of birth, and region, for all people included in the study. Furthermore, we estimated incidence rate ratios (IRRs) to estimate the crude association between urbanicity and psychosis. We used then Poisson regression to examine the association between urbanicity and FEP while controlling for potential confounders. Data was structured at the following ascending hierarchical levels: individuals, regions, and time (i.e., 2005-2022). Moreover, we ran the same models for males and females separately. All analyses were conducted in R (packages: "tidyverse", "janitor", "data.table", "gtsummary", "broom", "lubridate").

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Results

The study population comprised 5,137,561 individuals. Of those, we identified 14,410 with confirmed nonaffective FEP between 2005-2022. Among those with confirmed FEP, 66.25% were male, 33.75 % were females. People with FEP were diagnosed most frequently when they were between 15~19 (47.45%) and 20~24 (25.91%) of age. Given that the years of birth for this cohort ranged from 1992-2012, the youngest participant with FEP was 10 and the oldest 31 years old. When comparing people with vs without FEP, there were more males (66.25% vs. 51.01%) and people living in the Metropolitan Santiago Area (46.45% vs. 40.65%); differences on urbanicity were minimal between the two groups (88.33% vs. 88.60%).

Table 2 shows the crude FEP incidence rates by the variables of interest. Over a total of 91.96 million person-years, we observed a crude incidence rate of 15.67 cases per 100,000 person-years (95% confidence interval [CI]: 15.42-15.93). The incidence rate for males was higher than that for females, with 20.36 cases per 100,000 person-years (95% CI: 19.95-20.77) compared to 10.79 cases per 100,000 person-years (95% CI: 10.49-11.10) for females.

Table 2. Crude incidence rates* with 95% Confidence Intervals (CI)

	All participants	Urban	Rural
Sex at birth			
Male	20.33 (19.92, 20.73)	20.40 (19.97, 20.84)	19.73 (18.53, 20.92)
Female	10.79 (10.48, 11.09)	10.60 (10.28, 10.92)	12.25 (11.29, 13.20)
Year of birth			
Before 1997	26.31 (25.71, 26.90)	26.62 (25.97, 27.26)	24.24 (22.66, 25.83)
1998~2002	22.91 (22.26, 23.56)	23.03 (22.34, 23.72)	22.05 (20.22, 23.88)
2003~2007	8.95 (8.55, 9.36)	8.95 (8.52, 9.38)	8.97 (7.68, 10.25)
2008~2012	1.35 (1.20, 1.50)	1.32 (1.16, 1.48)	1.59 (1.06, 2.13)
Region at birth**			
Northern Region	13.33 (12.54, 14.12)	13.22 (12.42, 14.03)	16.80 (11.59, 22.00)
Central Region	17.62 (17.25, 17.98)	17.61 (17.23, 17.99)	17.78 (16.08, 19.48)
Central South Region	12.31 (11.84, 12.79)	11.80 (11.28, 12.33)	14.24 (13.12, 15.37)
Southern Region	15.18 (14.47, 15.89)	14.34 (13.52, 15.17)	17.18 (15.79, 18.56)
Southernmost Region	12.56 (10.73, 14.40)	12.57 (10.67, 14.47)	12.46 (5.41, 19.51)

*cases per 100 000 person-years

The urban incidence rate was slightly lower at 15.62 cases per 100,000 person-years (95%CI: 15.35-15.89) compared to the rural incidence rate of 16.06 cases per 100,000 person-

years (95%CI: 15.29-16.83). The rates varied across different regions, ranging from 13.3 to 17.6

cases per 100,000 person-years. Among these regions, the Central Region (Coquimbo,

Valparaíso, Metropolitan Santiago) had the highest incidence rate at 17.6 cases per 100,000

person-years (95% CI 17.25-17.98). Psychosis rates were higher in rural compared to urban

areas in Northern, Central South, and Southern regions (see Table 2).

We found a null association between urbanicity and nonaffective FEP in the unadjusted

(IRR: 0.97; 95%CI: 0.92 – 1.02) and adjusted models 1 (IRR: 1.06; 95%CI: 1.01 – 1.11) and 2

(IRR: 0.96; 95%CI: 0.91 – 1.01) (see Table 3). These results indicate that individuals who were

born in urban areas were not at higher risk of developing FEP than those who were born in rural

areas after controlling for the hypothesized confounders.

Table 3. Unadjusted and adjusted incidence rates ratios (IRR) for the urbanicity/psychosis association

	IRR	2.5%CI	97.5%CI
Unadjusted model			
Urbanicity	0.97	0.92	1.02
Adjusted model 1*			
Urbanicity	1.06	1.01	1.11
Year of birth	0.89	0.89	0.89
Adjusted model 2			
Urbanicity	0.96	0.91	1.01
Year of birth	0.89	0.89	0.89
Region at birth			
Central Region (Ref.)			
Northern Region	0.79	0.74	0.84
Central South Region	0.68	0.65	0.71
Southern Region	0.85	0.81	0.90
Southernmost Region	0.71	0.62	0.83

*Model 1: exposure: urbanicity; outcome: FEP diagnosis; adjusted for year of birth
*Model 2: exposure: urbanicity; outcome: FEP diagnosis; adjusted for year of birth and region

In analyses on gender differences, we detected a small association between being born

in an urban area and psychosis among males (IRR: 1.13; 95% CI: 1.06, 1.21), and a

nonsignificant trend among females in the opposite direction (IRR: 0.93; 95% CI: 0.85, 1.01),

after controlling for year of birth and region.

Discussion

We detected a null association between urbanicity at birth and nonaffective FEP in Chile. This study represents the most rigorous and comprehensive effort to estimate the effect of urbanicity on psychosis undertaken in the Global South.

The association between urbanicity and psychosis has been consistently reported in studies from the Global North, particularly Northern Europe (Lewis et al., 1992; Marcelis et al., 1999; Marcelis et al., 1998; Mortensen et al., 1999; Pedersen & Mortensen, 2001, 2004; Pedersen, 2006). For instance, Lewis et al. (1992) and Mortensen et al. (1999) reported 1.65-fold (95%CI: 1.19-2.28) and 2.40-fold (95% CI: 2.13-2.70) increased psychosis risk in Sweden and Denmark, respectively. In a meta-analysis, Vassos et al. (2012) estimated a pooled effect of 2.37 (95%CI: 2.01-2.81) for exposure to urban environment on the incidence of schizophrenia.

The results from the Global North may be partially explained by how urban environments can restrict the capabilities among certain groups, such as immigrants and people from minority backgrounds, who are often considered as high-risk groups for psychosis (Fusar-Poli, 2017). The elevated risks reported in these regions could reflect an interaction between urbanicity and social determinants that affect these groups disproportionately. Urban areas might concentrate risk factors that particularly affect immigrants and minority groups, such as social exclusion, discrimination, and reduced access to essential services, which can limit their opportunities and capabilities (Anand, 2018). These constraints could lead to increased stress and diminished social support, exacerbating the risk of developing psychosis. The heightened risk in urban settings might thus not be a direct product of population density or urban life per se but could be indicative of the social inequalities and the resultant capability deprivations that are more pronounced in these environments.

In contrast, findings from the Global South have been inconsistent, with several studies reporting null results. These studies include research conducted in Chile (González-Valderrama et al., 2020), Brazil (Del-Ben et al., 2020), India (Ganguli, 2000), Uganda (Lundberg et al., 2008), and China (Long et al., 2014). More recently, a multi-country case-control study found

that urbanicity increased psychosis risk in Trinidad and Tobago but not in Nigeria and India (Robert et al., 2023). However, we should interpret these results with caution due to several methodological limitations, including, but not limited to, unrepresentative samples, uncertainty in the incidence rates' numerator and denominator, simultaneous measurement of the exposure and outcome, and a lack of data on potential confounders, particularly parental antecedents (Robert et al., 2023). To address these limitations, we used data from the excellent Chilean national registries as noted previously.

The results from the Global South challenge the premise that being born in urban areas universally increases the risk of developing psychosis, including the findings from my study. This difference compared to the Global North may be explained through the lens of the Capability Approach: urban areas in the Global South may not subject individuals to the same degree of negative stressors or may even provide protective factors such as better access to mental health services or stronger community ties that mitigate the risk of psychosis. Hence, the urban experience in these settings, including Chile, could potentially support a wider range of positive capabilities that buffer against the development of psychosis.

Our findings derive from a similarly rigorous research program as the studies conducted in Northern Europe, which also relied on comprehensive and nationwide registries. In a recent review, I argue that population density, which is commonly used as a measure of urbanicity in most studies, may not capture the intricate and diverse characteristics of urban environments (Mascayano et al., 2023, thesis Chapter 2). Urban areas are complex ecosystems with a multitude of factors that influence individuals' experiences and enhance (or restrict) capabilities. Therefore, relying solely on standard measures, such as population density, might overlook important nuances regarding the effects of the multifaceted aspects of urbanicity. We need locally validated measures that align with the unique understandings and practices of specific regions to advance this field.

Although we did not detect an association in the whole study population, we did find an indication of a small differential effect of urbanicity on psychosis by sex, with urbanicity slightly increasing incidence in male but not females. These results align with a previous study by Marcelis et al. (1998), but other studies have yielded mixed results (Allardyce et al., 2003; Suokas et al., 2023; Sundquist et al., 2004). Despite the growing demand for more attention to gender differences in psychosis and urbanicity research, the reasons behind these differences remain unclear (Riecher-Rössler et al., 2018). A differential effect of urbanicity on psychosis between males and females could be seen as a reflection of the distinct capabilities and vulnerabilities each gender might experience in specific urban environments. Future research should employ a gender-specific approach to further examine the potentially distinct impact of urbanicity on psychosis risk among males and females (Haarmans, 2019).

Limitations

First, we need a more detailed conceptualization of urbanicity, considering crucial factors related to urbanicity (historical, contextual, social) rather than focusing exclusively on population density (Susser, 2021). While my current approach to defining urbanicity was appropriate for local context and considered social and housing indicators, future studies should incorporate measures that better characterize urban areas compared to semi-rural and rural areas. This would allow for a more comprehensive examination of the various aspects of urbanicity and their impact on psychosis. I have argued that the Capability Approach can provide a nuanced framework to understand urbanicity characteristics and effects in the broader context of human development and social justice. I suggest that future endeavors use this approach to conceptualize questions, guide measurement, and interpret results.

Second, differences between the reported results and previous studies may also be explained by methodological considerations, including the conceptualization of the exposure (e.g., population density versus population density combined with employment and housing

indicators), the timing of exposure measurement (e.g., upbringing versus birth), and the availability of data on potential confounders (e.g., parental antecedents of mental disorders). For instance, Danish research has reported that urban upbringing is a stronger predictor of urbanicity than urban birth (Pedersen & Mortensen, 2001). Moreover, parental antecedents, including socioeconomic status and diagnosis, have accounted for psychosis risk after controlling for confounding in some studies (Maxwell et al., 2021).

Third, future studies should also enhance our understanding of urban, semirural, and rural environments by embracing a broader range of sources and indicators. We should use and incorporate data from different sources, especially qualitative data, that delves into individuals' lived experiences (Söderström et al., 2016). By capturing individuals' lived experiences and understanding the real freedoms and opportunities they have (or lack) in urban versus rural settings, researchers can gain deeper insights into the complex interplay between urbanicity, psychosis risk, and related factors (Winz, 2018). These factors consider social aspects such as social fragmentation and deprivation, as well as environmental factors like air pollution and the presence of green spaces. While some of these factors have been studied in the Global North (Allardyce et al., 2005; Kirkbride et al., 2008; Newbury et al., 2018; Sariaslan et al., 2015; Veling et al., 2015; Zammit et al., 2010), almost no studies have examined their effects on psychosis in the Global South. As for urbanicity, one could expect large variation in terms of meaning and measurement of these factors in the Global South, which must be considered in future research.

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Examining the effect of parental social deprivation on the urbanicity/psychosis association

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Abstract

Background: The established association between urbanicity and psychosis in the Global North has not yet been observed in the Global South. From a Capability Approach perspective, urban areas have the potential to augment opportunities for mental well-being. However, they can also amplify risk if access to these opportunities is denied. This risk could be particularly substantial for marginalized families and individuals who experience social deprivation. This study, using registry-based data from Chile, aimed to examine the role of social deprivation as a moderator in the urbanicity-psychosis association.

Methods: I used registry-based data from two key sources: the Chilean First-Episode Psychosis (FEP) registry, covering cases from 2005 to 2022, and the Birth and Death registry, which has records dating from 1992 to the present. The analysis included a cohort of 5,137,561 individuals born in Chile between 1992 and 2012, with 14,410 confirmed nonaffective FEP cases identified between 2005 and 2022. The main exposure was urbanicity at birth and the main outcome was nonaffective FEP, and potential effect modifiers included two indicators of social deprivation: parental employment and education. I used Poisson regression to estimate Incidence Rate Ratios (IRR) and assessed interaction between urbanicity and social deprivation on the multiplicative and additivity scales.

Results: Results revealed an interaction effect of education of the mother and the father on both the multiplicative and additivity scales in the association between urbanicity and non-affective FEP. I did not find clear evidence of interaction between father employment and urbanicity, and between mother employment and urbanicity. These findings suggest that urbanicity at birth may have a more pronounced impact on individuals whose parents had limited education.

Discussion: I found evidence that parental low education, indicators of social deprivation, moderate the effect of urbanicity on psychosis in Chile. For instance, individuals whose parents had limited education and who lived in urban areas may have faced restricted opportunities for human development and mental health well-being, thereby increasing their risk of psychosis. Future research should consider other potential moderators (e.g., air pollution, crime) at both individual and community levels.

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Background

      The association between urbanicity and psychosis has been extensively studied in the

Global North (e.g., Western and Northern Europe). Researchers have proposed factors

commonly found in urban settings that may influence the strength and direction of this

association (Krabbendam et al., 2020; Fett et al., 2019). Some of these factors include

indicators of social deprivation such as parental unemployment and low education (Heinz et al.,

2013). While the evidence is emerging, the nature and effects of these potential moderators

require further examination, especially in the Global South (Africa, Asia, Latin America) where

research is scarce. The current study represents an important first step in addressing this gap,

using nationwide, registry-based data from Chile.

      The urbanicity/psychosis association is considered one of the most important

epidemiologic findings on environment and psychosis. Robust research programs have

consistently found that urbanicity increases the risk of non-affective psychosis after controlling

for individual- and group-level variables (e.g., mother's diagnosis of psychosis and regional

differences, respectively) (Lewis, et al., 1992; Marcelis et al., 1998; Mortensen et al., 1999;

Pedersen & Mortensen, 2006; Pedersen, 2006). In a meta-analysis, Vassos et al. (2012)

reported that individuals who were born and brought up in urban areas had over twice the odds

of developing psychotic disorders (e.g., schizophrenia) compared to people from rural areas

(OR=2.37; 95% CI: 2.01–2.81) (Vassos et al., 2012). Recent reviews (Fett et al., 2019;

Abrahamyam et al., 2020) and book chapters (Solmi et al. 2017) have summarized these

consistent results.

      Despite these results, we (Mascayano et al, 2023- Chapter 2), and others (Kirkbride et

al., 2018), have identified two major gaps in this field. First, research from the Global South has

yielded mixed results. In fact, several studies have reported a null association between

urbanicity and psychosis (Gonzalez et al., 2022; Del-Ben et al., 2019; Jongsma et al., 2020;

DeVylder et al., 2018), including our recent study based on data from national registries in Chile

(Mascayano et al., 2023). We have suggested that the urbanicity/psychosis association may not pertain to countries in the Global South, and, if it does, it may operate through different causal pathways. Second, the factor moderating the association between urbanicity and psychosis remain largely uncharacterized. We know little regarding how this association works and the role of other variables involved, including social deprivation.

I have used the capability approach by Amartya Sen (1985, 1999), and further developed by Martha Nussbaum (2000, 2011), to conceptualize the role of social deprivation as a potential barrier to develop capabilities in urban areas. The capability approach focuses on what individuals are effectively able to do and be, the quality of life they can achieve, and the freedoms they must have to lead the kind of life they value (Davidson, 2009; Hopper, 2007). It shifts the focus from mere resource availability to a person's ability to convert these resources into valuable activities and states. In understanding the association between urbanicity, psychosis, and social deprivation, the capability approach offers a novel perspective. Urbanicity may provide numerous resources and opportunities, but not everyone has the same capability to transform these resources into valuable functionings (e.g., being healthy, educated, employed, or participating in cultural and social activities). For instance, while urban areas might have more and better healthcare facilities, education systems, and employment opportunities, social deprivation can act as a significant structural constraint, preventing individuals from accessing and benefitting from these resources.

We define social deprivation as a condition in which individuals or communities lack access to essential resources and opportunities (APA, 2023). Extensive research has been conducted to understand the role of social deprivation in the onset of psychosis. Several studies have reported higher rates of psychotic disorders, including schizophrenia, among individuals with low social status, especially those with low socioeconomic status at birth (Kowk, 2014), and those residing in deprived neighborhoods (March et al., 2008). For example, Allardyce et al. (2005) reported that individuals living in the most socially deprived areas (e.g., overcrowding,

male unemployment) were five times more likely to experience psychosis compared to those in less deprived areas (IRR=5.29, 95%CI=1.49-18.75). Furthermore, Kirkbride et al. (2017) found that individuals entering early psychosis services had higher incidence rates of psychosis when they lived in neighborhoods with the highest unemployment rates (IRR=1.56, 95%CI=1.04–2.35). More recently, van der Ven and Susser (2023) have noted that structural racism is one of the main causes of the increased incidence of psychosis among Blacks compared to Whites in the U.S.

Various indicators of social deprivation may increase or decrease individuals' capabilities and thus modify psychosis risk in urban settings. These indicators encompass having parents who are unemployed and have low educational attainment, raising children in a single-parent household, receiving welfare benefits, having a low family income, residing in poor housing conditions, or having a low family socioeconomic status (Heinz et al., 2013). While some studies have reported a partial attenuation in the association between urbanicity and psychosis after controlling for these factors, the strength of this association remained predominantly unchanged (Spauwen et al., 2004; Lewis et al., 1992; Radua et al., 2018; Ku et al., 2021). However, most, if not all, of these studies have conceptualized social deprivation as a potential confounder and have adjusted for it in their regression analyses. To my knowledge, there has been no prior investigation on whether and how social deprivation interacts moderate the effect of urbanicity on psychosis risk.

I argue that social deprivation, as an important barrier for human growth and capability development, can exacerbate the impact of urbanicity on the risk of psychosis. As noted, urban areas often exhibit high levels of unemployment, low education, homelessness, and low income (Hubbard, 2017). These factors, when combined with urbanicity, might increase the risk of psychosis onset by triggering gene-environment responses (Krabbendam & van Os, 2005), and overwhelming an individual's coping mechanisms (Scheepers et al., 2018). In contrast, social advantages, as opposed to social deprivation, can increase individuals' opportunities for mental

well-being and quality of life and serve as protective factors against the development of psychosis (Fett et al., 2019). For instance, parents with higher levels of education are more likely to choose neighborhoods that have good schools and strong social support networks, which can lower the odds of their children developing psychosis. Likewise, parents who have jobs, especially competitive jobs, are often in a better position to afford a safe and supportive living environment in urban areas, which includes improved access to healthcare (Kirkbride et al., 2018).

I used registry-based data from Chile to examine the moderation role of social deprivation in the association between urbanicity at birth and psychosis. Chile is one the most prosperous countries in the Global South and has excellent healthcare and social systems (Bossert & Leisewitz, 2016). The mental health system has been praised as one of the most integrated and comprehensive systems in the Global South (Minoletti et al., 2012), with a unique program for people with early psychosis (Minoletti et al., 2021). However, Chile is a largely unequal country in terms of income and opportunities for employment and education (OECD, 2021b), which has been linked to worse health and mental health outcomes in Santiago and other large cities (Severino et al., 2021; Madero-Cabib et al., 2019). For instance, parental low education was the strongest predictor of depression and other common mental disorders in a community-based sample in Santiago (Araya et al., 2003). Therefore, although we found a null association between urbanicity and psychosis in a previous study in Chile (Mascayano et al., 2023), I hypothesized that urbanicity at birth may have an effect on psychosis if it acts in tandem with social deprivation based on parental unemployment and low education.

Methods

Study design and data sources

I have described the main features of the study population elsewhere (Mascayano et al., 2023- Chapter 2). In brief, this study utilized data from two key sources: the Chilean First-

Episode Psychosis (FEP) registry, covering cases from 2005 to 2022, and the Birth and Death

registry, which has records dating from 1990 to the present. The FEP registry includes

individuals suspected or confirmed to have FEP, offering detailed individual-level data such as

diagnosis, age, gender, admission information, place of residence, and socioeconomic status of

parents. The Birth and Death registry provides comprehensive information on births and deaths

in Chile, encompassing nearly the entire population. It records essential details about births,

including the newborn's national ID, height, weight, birth location, and parental educational and

employment information.

Study population

I established a cohort that includes individuals born in Chile between 1992 and 2012. To

identify those with FEP, I utilized the Chilean FEP registry described previously. To estimate

person-years, we used the complete historical cohort and the observation period from 2005 to

2022. Starting with an initial cohort of 6,977,202 individuals, I excluded participants who: 1)

were born before 1992 or after 2012 (n=1,798,973); 2) passed away prior to 2005 (n=40,631);

and 3) received a diagnosis before 2005 (n=37). In this cohort, the youngest participant with

FEP was 10 and the oldest 31 years old.

Measures

The main outcome of the study was a diagnosis of nonaffective FEP using ICD-10 codes

(F20–F29). The FEP registry includes both "suspected" and "confirmed" cases, but I considered

only "confirmed" cases as described in a prior study (Larach et al., 2022). The main exposure

was urbanicity at birth. To measure urbanicity, we used a binary "urban/rural" classification

provided by the National Institute of Statistics, which considers factors like population density,

housing, and employment (INE, 2019). This classification offers a locally relevant and nuanced

understanding of urbanicity beyond population density. Urban areas have over 2,000 inhabitants

or 1,001 to 2,000 inhabitants with fewer than 50% engaged in primary activities, while rural

areas have 1,000 or fewer inhabitants or 1,001 to 2,000 inhabitants with over 50% engaged in

primary activities. In this context, primary sector activities relate to activities whose end purpose

is in exploiting natural resources. I <u>controlled</u> for age (year of birth) and region because there

were differences in the exposure and the outcome by year of birth and region, as shown in

Table 1 and reported in our previous study (Mascayano et al., 2023 – Chapter 2). As noted in

Paper 2, I did not deem the other variables available as confounders.

Table 1. Characteristics of the study population

Variables	All participants (n = 5137561)		Urban (n = 4552194)		Rural (n = 585560)	
	N	%	N	%	N	%
Gender						
Male	2623047	51.06	2325555	51.09	297399	50.79
Female	2514365	48.94	2226317	48.91	287948	49.17
Undetermined	149	< 0.01	129	< 0.01	20	< 0.01
Year of birth						
Before 1997	1582833	30.81	1375666	30.22	207150	35.38
1998~2002	1165424	22.68	1023974	22.49	141274	24.13
2003~2007	1154263	22.47	1036751	22.77	117512	20.07
2008~2012	1235041	24.04	1115610	24.51	119431	20.40
Region at birth						
Northern Region	454,461	8.85	441,113	9.69	13,328	2.28
Central Region	2,794,980	54.40	2,662,983	58.50	131,913	22.53
Central South Region	1,161,450	22.61	918,313	20.17	243,074	41.51
Southern Region	646,641	12.59	454,942	9.99	191,675	32.73
Southernmost Region	80,029	1.56	74,650	1.64	5377	0.92
Paternal characteristics						
Education						
Basic, primary, or none	963237	18.75	682763	15.00	280441	47.89
High school or more	3602674	70.12	3375208	74.14	227351	38.83
Missing	571650	11.13	494223	10.86	77768	13.28
Employment*						
Inactive, unemployed, or retired	521094	10.14	479156	10.53	41923	7.16
Active	4382214	85.30	3864584	84.89	517452	88.37
Missing	234253	4.56	208454	4.58	26185	4.47
Maternal characteristics						
Education						
Basic, primary, or none	1178603	22.94	869996	19.11	308535	52.69
High school or more	3958894	77.06	3681953	80.88	276820	47.27
Missing			245	< 0.01	205	< 0.01
Employment*						
Inactive, unemployed, or retired	3693013	71.88	3172068	69.68	520807	88.94
Active	1444537	28.12	1379923	30.31	64559	11.03
			203	< 0.01	194	< 0.01

*Active = employed; Inactive = students, retired, pensioners

I selected two indicators of social deprivation as potential moderators: parental employment (0 = "Unemployed or retired" or "Inactive"; 1 = "Active") and education (0 = "None" or "Basic or Primary"; 1 = "High School", "College", or "Graduate"). These variables were available for both the participant's mother and father. Table 2 provides a description of each variable along with its categories. I kept the same names and definitions from the Chilean Ministry of Health codebook.

Table 2. Proposed social deprivation moderators.

Low Education	
Paternal education	0 = "None" or "Basic or Primary" 1 = "High School", "College", or "Graduate"
Maternal education	0 = "None" or "Basic or Primary" 1 = "High School", "College", or "Graduate"
Unemployment*	
Paternal unemployment	0 = "Unemployed or retired" or "Inactive" 1 = "Active"
Maternal unemployment	0 = "Unemployed or retired" or "Inactive" 1 = "Active"

*Active = employed; Inactive = students, retired, pensioners

Data analysis plan

I tested the association between urbanicity at birth and the incidence of nonaffective FEP, controlling for potential confounding by the year of birth and region, and assessing moderation effects of parental low education and unemployment. I conducted descriptive analyses for each variable of interest, including the exposure, outcome, confounder, and potential moderators.

To assess the association between urbanicity at birth and nonaffective FEP incidence, I used a Poisson regression model, following a similar procedure as per our previous study (Mascayano et al., 2023- Chapter 2). The outcome variable was the count of nonaffective psychosis cases, and the exposure variable was urbanicity at birth, categorized as urban or rural. Each model was adjusted for year of birth and region (see Tables 3 and 4).

For the multiplicative scale, the interaction effect was determined by summing and exponentiating the coefficients of the included variables (e.g., urbanicity, paternal education). In other words, I have calculated the expected Incidence Rate Ratio (IRR) for the combined effect of urbanicity and education or employment and compare it to the IRRs that would be expected if there were no interaction. The IRRs for the main effects are given by e^{B1} (urbanicity), e^{B2} (education or employment), while the IRR for the interaction is given by $e^{B1 + B2 + B3}$.

For the additivity scale, I used two measures: the Relative Excess Risk due to Interaction (RERI) and the Attributable Proportion. RERI can be calculated as: RERI = IRR_{11} – IRR_{10} – IRR_{01} + 1.

Where (I use education as example):

IRR_{11} is the incidence rate ratio for having both risk factors (urbanicity and low education)

IRR_{10} is the incidence rate ratio for having the first risk factor (urbanicity) and not the second (higher education).

IRR_{01} is the incidence rate ratio for not having the first risk factor but having the second (low education).

A RERI of more than 0 suggests additive interaction, meaning the joint effect of both exposures is greater than the sum of their individual effects. I have calculated 95% Confidence Intervals (CI) around RERI for a measure of precision.

The Attributable Proportion (AP) represents the proportion of the incidence among individuals exposed to both exposures (urbanicity and employment/education) that is attributable to their interaction. The AP can be calculated as: $RERI/IRR_{11}$. In terms of effect size, the AP can be thought of as indicating the strength of the interaction, where larger absolute values of AP suggest a stronger interaction.

I used the following R packages to conduct the aforementioned analyses: "tidyverse", "janitor", "data.table", "gtsummary", "broom", "lubridate."

Results

The study included a total of 5,137,561 individuals. Of those, I identified 14,410 individuals with confirmed nonaffective FEP during 2005-2022. Table 1 describes the main characteristics of the population in terms of gender, year of birth, and parental employment and education. The proportion of males and females was nearly the same in urban versus rural areas. However, there were some differences in age, with people in urban areas being slightly younger. Fathers in urban areas had higher levels of education compared to those in rural areas ("high school or more": 74.1% vs. 38.8%, respectively), but both groups had a similar employment rate ("active": 84.9% vs. 88.4%). Mothers in urban areas were significantly more educated ("high school or more": 80.9% vs. 47.3%) and had a higher likelihood of being employed ("active": 30.3% vs. 11.0%).

Table 3 shows the regression analyses examining parental education as a moderator in the urbanicity/psychosis association on the multiplicative scale. The IRR for the interaction between urbanicity and low paternal education was 1.32 (95% CI: 1.17, 1.48), indicating a multiplicative interaction. On the additive scale, the RERI was 0.23 (95% CI: 0.04, 0.42) suggesting that the combined risk from both city living and low paternal education is 23% more than the sum of their separate effects, when compared to rural location with higher parental education. Additionally, the Attributable Proportion of 0.17 implies that 17% of the incidence among those exposed to both factors was due to this interaction.

Table 3. Parental education as a moderator on the multiplicative scale

	IRR	95%CI	*P*
Model 1			
Urbanicity	1.03	0.94, 1.12	0.59
Year of birth	0.89	0.89, 0.89	0.00
Paternal education	1.06	0.95, 1.19	0.27
Region at birth			
Central Region (Ref.)			
Northern Region	0.89	0.76	0.86
Central South Region	0.78	0.75	0.81
Southern Region	0.85	0.84	0.91
Southernmost Region	0.72	0.64	0.85
Urbanicity and paternal low education vs. rural location and paternal higher education	1.32	1.17, 1.48	0.00

Model 1: FEP + urbanicity at birth + year of birth + region + paternal education + combined effect (urbanicity + paternal education)

Model 2			
Urbanicity	1.02	0.94, 1.11	0.67
Year of birth	0.89	0.89, 0.90	0.00
Maternal education	1.12	1.02, 1.24	0.02
Region at birth			
Central Region (Ref.)			
Northern Region	0.81	0.75	0.83
Central South Region	0.70	0.64	0.73
Southern Region	0.82	0.80	0.85
Southernmost Region	0.72	0.67	0.79
Urbanicity and maternal low education vs. rural location and maternal higher education	1.34	1.21, 1.49	0.00

Model 2: FEP + urbanicity at birth + year of birth + region + maternal education + combined effect (urbanicity + maternal education)

I found similar but even stronger evidence for maternal education alone. On the multiplicative scale, the combined effect (IRR = 1.34; 95% CI: 1.21, 1.49) was greater than what would be expected if the effects of urbanicity and education were independent (Table 3). On the additive scale, the positive RERI of approximately 0.33 (95% CI: 0.18, 0.47) indicates that the combined effect of urbanicity and low maternal education was 33% greater than the sum of their individual effects compared to rural location and higher education. The AP was approximately 0.24, suggesting that approximately 24% of the incidence of psychosis in individuals exposed to both urbanicity and low maternal education is due to the synergistic effect of these two factors together.

I found no evidence for interaction between paternal employment and urbanicity (see Table 4). However, there was interaction between maternal employment and urbanicity (IRR=1.30; 95% CI: 1.07, 1.58) on the multiplicative scale. On the additive scale, the positive RERI of approximately 0.18 (95% CI: -0.14, 0.51) suggests that there might be a positive additive interaction, but the CIs include 0, suggesting that the interaction effect is not statistically significant on the additive scale. Therefore, the evidence for interaction between mother unemployment and urbanicity was not appealing. Finally, the AP was approximately 0.14, meaning that 14% of the incidence of psychosis is attributable to the interaction between these urbanicity and maternal employment rather than to the sum of their individual effects.

Table 4. Parental employment as a moderator on the multiplicative scale

	IRR	95%CI	*P*
Model 3			
Urbanicity	1.06	1.01, 1.12	0.03
Year of birth	0.89	0.89, 0.89	0.00
Paternal employment	1.11	0.89, 1.39	0.34
Region at birth			
Central Region (Ref.)			
Northern Region	0.87	0.80	0.90
Central South Region	0.70	0.66	0.72
Southern Region	0.80	0.76	0.91
Southernmost Region	0.76	0.72	0.80
Urbanicity and paternal unemployment vs. rural location and paternal employment	0.96	0.76, 1.21	0.72

Model 3: FEP + urbanicity at birth + year of birth + region + paternal employment + combined effect (urbanicity + paternal employment)

	IRR	95%CI	*P*
Model 4			
Urbanicity	0.89	0.74, 1.07	0.22
Year of birth	0.89	0.89, 0.89	0.00
Maternal employment	1.23	1.01, 1.48	0.04
Region at birth			
Central Region (Ref.)			
Northern Region	0.73	0.69	0.78
Central South Region	0.65	0.62	0.72
Southern Region	0.82	0.79	0.88
Southernmost Region	0.70	0.68	0.75
Urbanicity and maternal unemployment vs. rural location and maternal employment	1.30	1.07, 1.58	0.01

Model 4: FEP + urbanicity at birth + year of birth + region + maternal employment + combined effect (urbanicity + maternal employment)

Discussion

I have examined the effect of social deprivation as a moderator in the association between urbanicity and psychosis in Chile, finding consistent evidence for interaction between the low education of mothers and fathers and urbanicity in the association with nonaffective FEP. There was also some evidence for interaction between maternal unemployment and urbanicity, but this was not conclusive. These results suggest that urbanicity, as a significant environmental factor in psychosis research, may have a more pronounced impact on individuals who have experienced parental social deprivation.

Social deprivation, as defined earlier, represents a condition where individuals or communities lack access to essential resources and opportunities. Within the Capability

Approach, this can be understood as a deprivation of essential capabilities, which are foundational to achieving well-being and leading a fulfilling life (Sen, 1985). While urbanicity itself may not directly result in an increased risk for psychosis, when viewed through the lens of the Capability Approach, the interplay between urbanicity and social deprivation on psychosis becomes more evident. Individuals residing in an urban environment but facing social deprivation might not have the capability to access quality healthcare, engage in meaningful employment, or benefit from a supportive social network, even if these resources are physically present in the vicinity. This lack of capabilities can enhance vulnerability to stressors, lead to feelings of marginalization, and subsequently increase the risk of psychosis.

While the association between urbanicity and psychosis has been consistently replicated in Northern and Western Europe, research from the Global South has yielded inconsistent results. Two studies of particular significance in this context deserve mention. Valderrama et al. (2022), using data from the Chilean FEP registry and census-based data, reported that regional population density showed no association with the incidence of nonaffective FEP after adjusting for several covariates, including age, sex, and multidimensional poverty (IRR:0.98; 95%CI: 0.88–1.10). Furthermore, our team (Mascayano et al., 2023- Chapter 2), utilizing data from the same cohort as in the present study (n=5,137,561), identified a null association even after controlling for year of birth and region (IRR:0.96; 95%CI: 0.91 – 1.01). Both studies are in line with research conducted elsewhere in the Global South, such as Brazil (Del-Ben et al., 2020) and Nigeria (Robert et al., 2023).

However, as highlighted in this report, urbanicity may still play a significant role in the context of psychosis in the Global South, particularly for socially disadvantaged individuals and communities. Valderrama et al. (2022) also explored the association between poverty at the regional level and psychosis. They observed that the rates were highest in both the most impoverished and the most affluent regions of Chile, with the most pronounced pattern evident in Chile's poorest regions. Like many countries in the Global South, Chile grapples with

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substantial and well-documented inequalities in income, educational and employment opportunities, and access to healthcare and social services (Rotarous & Sakellariou, 2017). Despite the presence of healthcare and social resources being more abundant in urban areas compared to rural ones (Castillo-Laborde et al., 2017), individuals from lower socioeconomic backgrounds and residing in deprived urban areas may have limited access to these resources and may have their capabilities affected. Instead, they may face heightened exposure to issues largely reported in cities such as violence, crime, environmental pollution, and overcrowding in comparison to their rural counterparts (Heinz et al., 2013).

In my study, I found that parental education was a more important moderator than parental employment in the association between urbanicity and psychosis. The Capability Approach posits that better-educated parents are likely to possess a broader set of capabilities, which they can impart to their children. This endowment equips the offspring with superior resources to cope with the challenges of urban living, potentially mitigating the risk of psychosis. Unfortunately, local research has highlighted enormous inequalities in education. Based on a recent report, 62% of Chileans from the upper 20th percentile in income attend university, while only 21 percent attend from the lower 20th percentile (Logan, 2017). Moreover, about 75,000 of Chile's children are not in the school system, and most of those children are among the country's poorest (United Nations Women, 2021). Similar figures can be found in other countries in the Global South.

In response to this gap, many governments, including the Chilean government, have underscored that education is the primary mean to overcome poverty and social deprivation (Mshoro, 2012). Over the past few decades, Chilean parents have been encouraged to ensure their children receive a proper education to enhance their socioeconomic status (Cox, 2004). Nevertheless, access to higher education has become increasingly challenging for the most economically disadvantaged populations. Parents facing social deprivation often accumulate substantial debts to finance a university degree, and such a degree no longer guarantees a

high-paying job in the future (Marambio-Tapia, 2017). Consequently, parents with lower levels

of education, along with their children and communities, may experience a sense of social

confinement and helplessness, leading to increased stress and contributing to the emergence of

psychotic disorders.

In my study, I also found some evidence for interaction between mother employment

and urbanicity. Despite higher earnings and better job prospects for fathers (OECD, 2021a),

Chilean mothers frequently serve as the primary household earners (Garcés & Soto, 2017).

Being the main income provider means that maternal unemployment may directly translate to a

loss of the family's primary financial support and severe economic deprivation, increasing the

family's vulnerability to the negative aspects of urban living and decreasing the opportunities to

develop capabilities. Moreover, as it has been widely reported, the emotional burden on

mothers who are the primary breadwinners can be substantial when they become unemployed.

The stress associated with failing to fulfill the expected role of provider can have detrimental

effects on their mental health, which is closely linked to the mental and emotional well-being of

their children (Radua et al., 2018). However, as the evidence is inconclusive, further

examination is warranted.

Limitations

I note some limitations of my study and suggest areas for future research. First, in terms

of data availability, I lacked measures at the regional or neighborhood level to assess social

deprivation. Although Chile has a longstanding tradition of conducting national surveys on

poverty, housing, and other crucial social indicators (Valderrama et al., 2022), I could not

access this data in time for this report. Future research should aim to provide a comprehensive

understanding of the context by using aggregated data, which could enhance our findings

beyond the scope of individual-level indicators.

Second, while social deprivation is a relevant moderator in the association between urbanicity and psychosis, we should also consider other potential moderators, particularly those that can be obstacles for individuals to develop capabilities. These may encompass social factors like social fragmentation, social capital, crime, discrimination, and violence, (Krabbendam et al., 2021). Furthermore, some have proposed that these factors could act as either moderators or mediators depending on the causal scenario. Therefore, more research into the underlying mechanisms of the urbanicity-psychosis relationship is warranted.

Third, proposed moderators like social deprivation might be better understood and measured at the neighborhood level as suggested and implemented in studies conducted in the Global North (Solmi et al., 2020). Examining these factors within neighborhoods could advance this line of research in the Global South.

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Conclusions

I have conducted three studies exploring different aspects of the urbanicity-psychosis association. The first was a qualitative systematic review of the conceptualizations and operationalizations of urbanicity in psychosis research. The second examined the association between urbanicity at birth and nonaffective FEP using registry-based data from Chile. The third analyzed the role of parental social deprivation as a mediator in the urbanicity-psychosis relationship. Taken together, these studies highlight several key themes:

1. Urbanicity as a Multifaceted Construct: Urban living is not a singular experience; it is shaped by various contextual, cultural, and political factors, such as overcrowding, social deprivation, and political participation. The findings from the first paper illustrate that urbanicity is a heterogeneous concept that requires a multidimensional operationalization to capture its true essence and effects on mental health.

2. Social Inequalities as Moderators: The profound influence of social deprivation on the urbanicity-psychosis association was evident in the Chilean context. The moderating role of parental education, in particular, points to broader systemic issues of inequality that influence health outcomes. This interaction underscores the need for future research on casual mechanisms involving social deprivation and other factors.

3. Cultural and Regional Specificity: The distinct outcomes observed in Chile compared to those in Northern Europe highlight the need for culturally and regionally sensitive research. These differences call for a reexamination of existing theories and models of psychosis that have been largely developed in the Global North and may not be universally applicable.

4. Implications for Public Health Policy: The findings from these studies have significant implications for public health policy, especially in the Global South. They suggest that urban planning, education, and healthcare policies must be intertwined to mitigate the risks associated with urban living. By addressing social inequalities and enhancing the

capabilities of urban residents, policymakers can create environments that promote

mental health and well-being and reduce the risk of mental health conditions.

5. <u>Generalizability of results</u>. While the findings shed valuable light on the urbanicity-

psychosis association within Chile, I have noted that no other country in the Global

South has such rich, national data. This inherent limitation underscores the need for

cautious interpretation and adaptation of these findings to different regions and cultures.

The multifaceted nature of urbanicity, the moderating role of social deprivation, and the

cultural and regional specificity highlighted in this research emphasize the importance of

conducting context-specific studies in diverse settings. However, the conceptual

framework and methodological approaches employed in this dissertation can provide

inspiration for future studies in other settings, encouraging researchers to adapt and

extend these methodologies to gain a deeper understanding of the urbanicity-psychosis

association in their specific contexts. For instance, Brazil and Colombia, with access to

reliable data from ongoing cohort studies and local registries, offer potential avenues for

exploring some of these questions in other Latin American settings.

6. <u>Future Directions</u>: My research points to several future directions, including the need for

mixed-method studies that can unravel the temporal dynamics of the urbanicity-

psychosis relationship. Methods and strategies from other fields such as anthropology,

urbanism, and architecture can provide a deeper understanding of the lived experiences

of individuals in urban environments. There is also a call for more nuanced measures of

urbanicity and social deprivation that can capture the complexities of these constructs.

Furthermore, integrating individual-level data with community-level data can offer a more

comprehensive understanding of urbanicity and associated factors. In Chile, a good

example is the Chilean Biennial National Socioeconomic Characterization Survey, a

nationwide, census-like, household survey covering several community-level social

factors such as social deprivation and social cohesion/fragmentation, as well as level of

violence, proportion without social security, deficits in basic services, overcrowding and poor structural housing quality, education, and employment.

The findings from these studies also speak to the importance of adopting a more comprehensive framework for understanding the impact of urban living on mental health, specifically the value of using the Capability Approach. As noted previously, this approach allows us to move beyond the traditional indicators of urbanicity and related factors, such as social deprivation, which often fail to capture the full breadth of individuals' lived experiences and the societal structures that shape these experiences in urban environments. For instance, whereas typical measures may note that a person lives in a high-poverty urban area, the Capability Approach asks what this person is actually able to do or be in this environment. It examines whether they have access to quality education, whether they can engage in meaningful employment, or if they have the freedom to enjoy recreational spaces and community programs that promote mental health.

By focusing on capabilities, we can explore how urban environments can either constrain or enhance these real freedoms, which is a more holistic way of understanding the interplay between environment and well-being. Consider a scenario where two individuals, both residing in a densely populated urban area characterized by high rates of unemployment and violence, have similar socio-economic profiles. Traditional frameworks of social deprivation would suggest they have an equal risk of developing psychosis. However, if one individual has access to a supportive social network and to mental health services, their capabilities and thus their potential resilience to psychosis are significantly different from the other individual who lacks these resources. The ability to be part of a community, to work in a stimulating environment, or to access mental health care when needed are all capabilities that can mitigate the impact of urban stressors on mental health.

In conclusion, these studies contribute to a paradigm shift in our understanding of the urbanicity-psychosis association. They urge researchers to adopt a more nuanced approach that considers the interplay of environmental exposures, social determinants, and individual capabilities. As urban populations continue to grow, especially in the Global South, the urgency to understand and address the factors that contribute to psychosis in urban settings becomes increasingly paramount. The insights provided by these studies not only inform the academic discourse but also offer tangible pathways for creating more equitable and mentally healthy urban societies. Furthermore, the limited research conducted in the Global South compared to the Global North highlights the need for further investigation in these settings, particularly in places where well-designed studies can be conducted. Future research should employ administrative data and locally validated measures wherever available. Overall, addressing the limitations of the existing literature will provide a more comprehensive understanding of the relationship between urbanicity and psychosis globally and inform effective prevention and intervention strategies.