Inequities in drug use and successful interventions: Umbrella study and analysis of emerging trends in Canada during the COVID-19 pandemic

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Abstract

Background: Current evidence suggests that certain subpopulations, such as ethnic or sexual minorities, bear a disproportional burden of population illicit drug use and related comorbidities. With drug use being a major risk factor for many chronic and acute diseases, addressing such an important health determinant could reduce health disparities prior to their clinical manifestation. This is especially relevant in the context of the stress and uncertainty associated with the COVID-19 pandemic, which, according to emerging research, may have led to increased drug use as a coping mechanism, potentially exacerbating sociodemographic disparities in drug use and associated comorbidities further. Given this context, it is pertinent to examine the effectiveness of illicit drug policies, and drug use trends during the COVID-19 pandemic with at-risk subpopulations and common risk factors in mind.

Objectives: Firstly, this thesis aimed to assess the current state of evidence from systematic reviews pertaining to the effectiveness of illicit drug policy interventions among subpopulations, using the PROGRESS-Plus framework to classify relevant common disadvantage factors. A second objective was to investigate risk factors associated with an increase in both licit and illicit drug use and unmet need for care during the COVID-19 pandemic in Canada. The overarching objective of the thesis was to assess subpopulation representation in systematic reviews and identify those who faced the most excess drug use and service accessibility challenges during the COVID-19 pandemic in Canada.

Methods: For the first objective, Manuscript 1 utilized umbrella review methodology. Three databases were searched for systematic reviews and meta-analyses. The data was double extracted, and quality of included studies was assessed using AMSTAR 2. Due to heterogeneity, the results were presented narratively in subgroups of relevant adapted PROGRESS-Plus domains. The second objective was addressed in Manuscript 2 using The Canadian Perspectives Survey Series 6 (CPSS6) from Statistics Canada and a set of binomial logistic regressions.

Results: Firstly, our evidence suggests that targeted interventions, such as culturally adapted drug reduction and prevention programs, are more represented in systematic reviews of subpopulation-specific illicit drug intervention evaluations and appear to work better for most subgroups at-risk than universal interventions or standard treatment. Secondly, we found no

existing systematic reviews that evaluate the effectiveness of drug policies for four domains: low social capital, disability, unemployment, and religion, despite evidence suggesting greater risk of drug use among these subpopulations. Thirdly, our exploration of drug use change in Canada during COVID-19 showed that increased opioid and non-prescription drug use was significantly associated with lower mental health scores. Inability to access needed social services was associated with being in poor mental health and being single, divorced, or widowed, as opposed to being in excellent mental health, and living in a marital, or conjugal relationship.

Discussion: Our findings suggested that subpopulations generally respond better to targeted, as opposed to universal interventions, pointing to the need to think about 'targeting within universalism', to ensure optimal population health outcomes. Most of the included reviews evaluated specific intervention types separately, as opposed to providing a comparative evaluation of targeted versus universal program effectiveness for different subgroups. Future research should aim to fill this gap. This is especially pressing as we emerge from the COVID-19 pandemic, which, as our initial findings suggest, may have disproportionately affected drug use trends and ability of certain subpopulations to find help for substance misuse.

Résumé

Contexte: Les données actuelles suggèrent que certains sous-groupes de la population, tels que les minorités ethniques, portent un fardeau disproportionné de consommation de drogues et de comorbidités connexes. La consommation de drogues étant un facteur de risque majeur pour de nombreuses maladies chroniques et aiguës, s'attaquer à un déterminant de la santé aussi important pourrait réduire les disparités en matière de santé avant leur manifestation clinique. Cela est pertinent dans le contexte d'incertitude lié à la pandémie de COVID-19, qui, selon des recherches émergentes, pourrait conduire à une augmentation de la consommation de drogues en tant que mécanisme d'adaptation, exacerbant potentiellement les disparités en santé. Par la suite, il est pertinent d'examiner l'efficacité des politiques en matière de drogues et les tendances en matière de consommation de drogues pendant la COVID-19 en gardant à l'esprit les sous-populations à risque.

Objectifs: Tout d'abord, cette thèse visait à évaluer l'état actuel des connaissances issues de recensions systématiques relatives à l'efficacité des interventions en matière de consommation de drogues parmi les sous-populations à risque. Un deuxième objectif était d'étudier les facteurs de risque associés aux changements dans la consommation de drogues licites ou illicites et les comportements de recherche d'aide au Canada pendant la pandémie de COVID-19.

Méthodes: Pour le premier objectif, le manuscrit 1 a utilisé une méthodologie d'examen général. Trois bases de données ont été utilisées pour des revues systématiques. En raison de l'hétérogénéité, les résultats ont été présentés de manière narrative dans les sous-groupes de domaines PROGRESS-Plus. Le deuxième objectif a été abordé dans le manuscrit 2 à l'aide de la série 6 d'enquêtes sur les perspectives canadiennes (SCSP6) de Statistique Canada et d'un ensemble de régressions logistiques binomiales.

Résultats: Premièrement, nos preuves suggèrent que les interventions ciblées, telles que les programmes de réduction et de prévention des drogues adaptés à la culture d'une sou-population, semblent mieux fonctionner pour la plupart des sous-groupes à risque que les interventions universelles ou le traitement standard. Deuxièmement, nous avons constaté que des revues systématiques existantes ne permettent pas d'évaluer l'efficacité des politiques en matière de drogue pour quatre domaines PROGRESS-Plus : faible capital social, handicap, chômage et

religion, malgré des preuves suggérant un plus grand risque de consommation de drogues parmi ces sous-populations. Troisièmement, notre exploration de l'évolution de la consommation de drogues au Canada pendant la COVID-19 a démontré qu'une consommation accrue de drogues était associée à une mauvaise santé mentale. L'incapacité d'accéder aux services de toxicomanie nécessaires était associée à une mauvaise santé mentale, et au statut de célibataire par opposition à une excellente santé mentale et au statut de marié, respectivement.

Discussion: Nos résultats suggèrent que les sous-populations répondent généralement mieux aux interventions ciblées qu'aux interventions universelles, soulignant la nécessité de réfléchir au « ciblage dans le cadre de l'universalisme », pour s'assurer d’une santé populationnelle optimale. Toutefois, la plupart des revues incluses évaluaient uniquement des types d'intervention spécifiques, au lieu de fournir une évaluation comparative de l'efficacité du programme ciblé par rapport à l'efficacité universelle pour différents sous-groupes. Les futures études devraient viser à combler cette lacune, tout en reconnaissant la nécessité d'évaluer les interventions pour les sous-populations que nous avons identifiées comme sous-représentées. Cela est urgent, d’autant plus que nous sortons de la pandémie, qui, comme le suggèrent nos résultats, peut avoir affecté les habitudes de consommation de drogues et la capacité de certaines sous-populations à trouver de l'aide pour l'abus de substances.

Contribution of Authors

I, Michaela Bunakova, conceptualised the objectives and studies design, drafted the full thesis, inclusive of all manuscripts and supporting chapters. I was responsible for developing and conducting all systematic searches and analyses included in this thesis.

Dr. Amélie Quesnel-Vallée supervised the production of this thesis and was involved in the studies' conceptualisation and design, editing, providing feedback and suggestions for all manuscripts, and supporting chapters along the whole production process.

Dr. Alissa Koski was an active member of the thesis committee, provided feedback on the conceptualisation and design, and revised all manuscripts and supporting chapters of this thesis critically for important intellectual content.

Kaitlin Conway performed the role of a second peer-reviewer for study selection and data extraction in Manuscript 1.

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I dedicate this thesis to my dad, Martin, who fought especially hard with a tiny, deadly tick last summer to stay with us and, hopefully, bear witness to my yet another graduation!

Table of Contents

List of Tables

Chapter 2: Literature Review

Chapter 3: Manuscript 1

Chapter 4: Manuscript 2

List of Figures

Chapter 3: Manuscript 1

Chapter 4: Manuscript 2

List of Appendices

Chapter 3: Manuscript 1

Chapter 4: Manuscript 2

List of Abbreviations and Acronyms

- **AIDS** Acquired Immune Deficiency Syndrome
- **CPSS6** Canadian Perspectives Survey Series 6
- **DARE** Database of Abstracts of Reviews of Effects
- **ED** Emergency department
- **HIC** High-income countries
- **HIV** Human immunodeficiency virus
- **LFS** Labour Force Survey
- **LMIC** Low- and middle-income countries
- **NPD** Non-prescription drugs
- **OECD** Organization for Economic Cooperation and Development
- **OR** Odds ratio
- **PICOS** Population, Intervention, Comparison, Outcome and Study Design
- **PROGRESS-Plus** Place of residence, Race, Occupation, Religion, Education, Socioeconomic status, Social Capital, Plus
- **PUMF** Public Use Microdata File
- **PWID** People who inject drugs
- **RCT** Randomized controlled trial
- **SES** Socioeconomic status
- **SUD** Substance use disorder
- **TDLE** Time-dependent life events
- **WHO** World Health Organization

Chapter 1: Introduction

Illicit drug use is a pressing public health problem both in Canada and globally. It represents a major risk factor for many chronic and acute diseases, including cardiovascular diseases, cancers, and overdose- or accident-related injuries (Petrovic et al. 2018). Approximately 0.6% of the world population, or 27 million people, regularly use illicit drugs, inclusive of narcotics, stimulants, depressants and hallucinogens (Dasgupta 2017, Houck and Siegel 2010). Moreover, it is well established that illicit drug use is not evenly distributed across different population strata. Those most at risk are likely to be non-white individuals (notably in the U.S.; McCabe et al. 2007), of lower socioeconomic status (Patrick et al. 2012), and display a range of important comorbidities, such as mental health disorders (Burns et al. 2004) or chronic pain (NIDA 2020a).

These factors commonly contribute to the stigmatization of illicit drug users, their discrimination, chronic stress, and barriers to accessing care, which further exacerbate the existing socio-demographic disparities in health and social outcomes associated with drug use (Ahern, Stuber, and Galea 2007). This issue has never been more pressing than today, in the context of the COVID-19 pandemic and its upcoming aftermath, for emerging research suggests not only that drug use increased overall, but that some subpopulations, such as ethnic, gender or sexual minorities, were disproportionately affected by illicit drug use during the pandemic (Khatri et al. 2021).

It is, therefore, pertinent to comprehensively examine existing drug interventions using best available methods, while remaining sensitive to the fact that their effectiveness may not be uniform across the population.

The objective of my thesis is to assess the available evidence from peer-reviewed systematic reviews and meta-analyses for the effectiveness of non-pharmaceutical illicit drug use interventions among different subpopulations and map the changes in both illicit drug use as well as legal consumption of opioids for pain management, and available help for misuse during COVID-19 in Canada, controlling for common sociodemographic drug use risk determinants. In so doing, I aim to provide a useful overview of current evidence and potential gaps to future researchers and decision-makers aiming to reduce illicit drug use equitably, while also curbing associated social disparities in health outcomes and related comorbidities, in Canada and beyond.

Thesis Organization

The main body of the thesis consists of four chapters. Chapter 2 offers a brief literature review on inequities in illicit drug use and specific approaches to policy interventions. In this chapter, I also provide a brief overview of recent research on illicit drug use patterns in the light of the ongoing COVID-19 pandemic. Chapter 3 contains Manuscript 1, an umbrella review of reviews, looking at the extent to which published systematic reviews on the effectiveness of illicit drug policies evaluate their outcomes with respect to different subpopulations with relevant PROGRESS-Plus characteristics. Chapter 4 includes Manuscript 2, an empirical chapter, the objective of which is to explore the extent to which different subpopulations are disproportionately affected by COVID-19 pandemic in their drug use patterns overall and resources available for misuse treatment in Canada. Chapter 5 contains a discussion of my results and their relevance for policy development and future research. This chapter also includes a summary section and concluding remarks.

Chapter 2: Literature Review

Preface

In this chapter, I provide an overview of the existing research on policy intervention design types and how they relate to existing health and social inequities within a broader population. I also delve deeper into existing evidence for differential illicit drug use and drug-use-related health outcomes among subpopulations and minorities, exploring both empirical evidence and potential explanatory factors for these outcome differences. Following that, I explain the adapted PROGRESS-Plus Framework, and discuss its relevance for this thesis as a tool to classify different subpopulations that may be disproportionately affected by illicit drug use compared to the general population, as well as underrepresented in high-quality research evidence most likely to yield policy change. Lastly, I touch upon the most recent evidence on the illicit drug use patterns and changes during the COVID-19 pandemic.

Policy interventions: Beyond traditional universalism

Despite unprecedented improvements in life expectancy and quality of life around the world over the last two centuries, researchers, decision-makers, and medical professionals are increasingly aware that these population-level improvements are not distributed equally across all members of our societies. This is particularly pressing as we undergo epidemiological and demographic transitions globally, where the spread of population aging will result in increasing burden of communicable diseases, often in addition to persistent significant burden from infectious diseases. Considering these changes, our existing public policies, health, and social services are facing growing pressures and scrutiny for efficiency, and increasingly, fairness.

To date, comparative health policy scholars and social epidemiologists have continuously attempted to improve our conceptualization and classification of public policies, building upon a myriad of interdisciplinary approaches, from building welfare regime typological frameworks, such as Esping-Andersen's 'three worlds of welfare capitalism', to classifying political economy determinants of health inequalities (Esping-Andersen 2013, Bambra 2011). Most policy frameworks, however, have been examined under the umbrella of a dichotomous categorization of policies as either 'universal' or 'targeted'.

To meaningfully contribute to this debate and to avoid any ambiguities resulting from the myriad of available definitions for these two policy categorizations, I will briefly describe both. Throughout this thesis, following Carey and colleagues, a 'universal intervention' can belong to one of two types, namely 'general' and 'specific' universalism. (Carey, Crammond, and De Leeuw 2015). A 'general universalism' can be defined as a service provided to the whole population within a given jurisdiction, regardless of individual characteristics with impartial determination of welfare recipients and allocation of benefits (Carey et al. 2015). An example of such a universalism could be state-wide sanitation measures. A 'specific universalism' does not necessarily guarantee universal access, but rather provides a means to extend social rights, such as the right to education or health care, as a way of achieving impartiality (Carey et al. 2015).

Targeted interventions, on the other hand, are provided to selected groups of individuals based on their specific characteristics, such as a geographic location, minority subpopulation membership

or employment status. Here, selectivism in targeting refers to designing and implementing specific policies for different groups based on their need. It can be either negative, or positive, whereby the former targets selection on the basis of means testing, while the latter provides additional services based on need (Carey et al. 2015). It is important to note, however, that this dichotomization of policies is a purely conceptual distinction and in practice, the contrast between the two is far less clear. In this context, it is important to understand the existing debate and how it relates to the increasing blurring and merging of the two policy design conceptualizations.

Marc Lalonde's 1974 report '*A new perspective on the health of Canadians'* and Geoffrey Rose's 1985 paper, '*Sick Individuals, and Sick Populations'* both planted valuable seeds for an ongoing debate related to the 'targeted' versus 'universal' public health intervention design. Lalonde argued that exposure to 'self-imposed' health risk behaviors and certain biological markers, such as smoking, obesity or high blood pressure, should play a role in determining at-risk populations, on which our public health interventions should be focused (Lalonde 1974). Geoffrey Rose provided a valuable typological distinction between individual- and population-level causes of illness (Rose 1985). Contrary to Lalonde, he offered a strong conceptual case for a population-level prevention strategy regardless of individual-level variation in risk. He argued that most cases of major health problems come from those at 'moderate risk' of disease, and reducing the risk a little in the whole population could prevent more cases than reducing it a lot among high-risk individuals (Rose 1985). Rose claimed that high-risk approaches, such as Lalonde's, fail to acknowledge the environmental conditions that affect disease incidence, while his population-level approach addresses both underlying causes of disease, and the shape of population disease distribution (Rose 1985).

Since then, social, and political epidemiologists, public health scholars, and sociologists have come a long way, but the ideas of Lalonde and Rose still resonate both among theoretical scholarship and health policy decision makers. In 2008, Frohlich and Potvin acknowledged the merits and limitations of both Lalonde's 'targeted', and Rose's 'universal' intervention design, while offering a third policy alternative focused on complementing universal population

approaches by addressing the underlying conditions and needs of vulnerable populations[1] (Frohlich and Potvin 2008). According to Frohlich and Potvin, Lalonde's targeted approach based on identifying and focusing on at-risk populations with modifiable health risk behaviors may lead to stigmatization and victimization of these groups (Frohlich and Potvin 2008). On the other hand, population approach interventions, such as those suggested by Rose can exacerbate existing health disparities and fail to address multiple risk exposures, or the mechanisms through which the distributions of risk exposures differ across population subgroups (Frohlich and Potvin 2008).

The approach suggested by Frohlich and Potvin attempts to combine the merits of both targeted and universal intervention strategies into a model that targets vulnerable groups within a universal policy solution. Such a 'targeted universalist' approach exploits both Rose's observation that to reduce disease on a population level, it is most effective to address more moderate-risk, rather than fewer high-risk individuals and Lalonde's appreciation for the need to address the most at-risk groups. It offers a solution that decreases unfair and avoidable health disparities between socially defined groups, while still shifting population risk distribution towards a lower average by addressing overall environmental conditions associated with increased risk (Frohlich and Potvin 2008). The approach also resonates well with proponents of Sen's 'Capabilities' normative framework, because by embedding targeting elements within univeral policies, we acknowledge the existence of differential capabilities to access and respond to the same amount of health promotional efforts (Frohlich 2010).

Over the last decades, for example, we saw differential response to smoking and tobacco use reduction interventions across different social and demographic strata and a notable socioeconomic gradient in the risk of smoking. This shows that public health innovations and health promotions are often first taken up by the most privileged, leaving their disadvantaged peers behind (Frohlich 2010). As a result, while we saw substantial population-level reductions in the prevalence of

[1] In this thesis, I will adopt Frohlich and Potvin's conceptualization of vulnerable populations, defined as:

> '…those, who concentrate numerous risk factors throughout their life course because of shared fundamental causes associated with their position in the social structure'
>
> (Frohlich and Potvin 2008)

However, to avoid perpetuating victimization through linguistic choices, I will refer to these groups as 'subpopulations at-risk', instead of 'vulnerable populations'.

smoking and tobacco use, we also witnessed growing soceioeconomic disparities in smoking and related comorbidities, increasing social unacceptability of smoking, stigmatization and association with low social class (Graham 2012).

To address such complex health issues with both a prevalence distribution and intervention effectiveness following a socioeconomic gradient, a cogent policy framework needs to be developed. With this realization, the Strategic Review of Health Inequalities in England, commonly known as 'The Marmot Review', added the concept of 'proportionate universalism' to the ongoing debate about equitable policy frameworks (Marmot 2010). The review argued for implementation of universal, rather than targeted policies, but with the understanding that the scale and intensity of the treatment should be proportionate to different levels of disadvantage among individuals (Marmot 2010). While the Marmot Review and its principle of proportionate universalism has been very influential in the academic community over the last 10 years, Carey, Crammond and De Leeuw note that despite its popularity, the principle, as conceptualized, is too general and ambiguous to be useful for practice (Carey et al. 2015). According to them, this ambiguity has led to varying interpretations of the meaning, such as Canning and Bowser's suggestion that proportionate universalism would see separate interventions for the most disadvantaged, or Birch's dose-response interpretation (Canning and Bowser 2010, Birch 2010). Such inconsistency in interpretation makes it unclear whether the principle calls for higher doses of the same interventions for at-risk populations, or whether new programs should be implemented to address differential need across the gradient (Carey et al. 2015).

Carey and colleagues argue that in order for proportionate universalism to flatten the social gradient in health, it needs to incorporate both elements of universalism (i.e. general and specific universal policies) and targeting based on principles of positive, needs-oriented selectivism (Carey et al. 2015). A successful framework for proportionate universalism should protect social rights against a purely income-based targeting, while improving upon and embracing the impartiality associated with universalism (Carey et al. 2015). Lastly, it must be noted that an effective approach requires a degree of particularism in the intervention design, for it is well understood that 'more of the same' may not work for different subpopulations and may even increase, rather than decrease health inequities (Carey et al. 2015). Such is the above-mentioned example of smoking

and the expanding use of downstream mass-media and workplace cessation interventions, which, according to Lorenc and colleagues follows this peculiar 'inverse prevention law' (Lorenc et al. 2013).

It is, therefore, crucial that we consider the complex ways in which subpopulations differ and examine possible mechanisms that cause the observed variation in intervention effectiveness across different population strata. Taking up this challenge, Burlew and colleagues expand upon a thought experiment developed by Miller et al. (Burlew et al. 2013). They imagine a healthcare-setting scenario, in which you, an ill patient, encounter a doctor that has been treating all patients using the same method and administering the same medication dose regardless of patient characteristics, such as age or pre-existing conditions, for over 30 years (Burlew et al. 2013). Burlew asks us whether we would be happy to return for a second visit and notes that this analogy is similar to the dilemma faced by many decision-makers and substance abuse care providers who are deciding on implementing an intervention with unknown efficacy for one subgroup of interest but demonstrated efficacy for another group (Burlew et al. 2013). This analogy highlights the growing appreciation of individual-level differences and subpopulation characteristics that now extends beyond the field of personal medicine and into the forefronts of health policy design.

In Canada, improving population health while reducing health inequities, otherwise known as 'levelling up', is an important part of the public health mandate (National Collaborating Centre for Determinants of Health 2013). To effectively 'level up' with regards to illicit drug use in the Canadian population, decision makers must understand and evaluate existing evidence and decide on implementing interventions across a continuum of potential approaches, including universal, targeted and blended approaches such as targeted or proportionate universalism in policy making (National Collaborating Centre for Determinants of Health 2013). The National Collaborating Centre for Determinants of Health in Canada acknowledges the challenges and limitations associated with both universal and targeted approaches, while noting that blended approaches could address both health gradients and health gaps (National Collaborating Centre for Determinants of Health 2013).

Illicit drug use, subpopulations, and disparities

We can apply some of the principles derived from the study of tobacco-use policies to that of illicit drug use. Even though illicit drug use significantly differs from smoking and tobacco use in many regards, most notably in its illegality across the whole population, risk of prosecution, overdose, or fatal injuries, we can nonetheless observe similar phenomena, such as stigmatization and a socioeconomic gradient in associated risks (Patrick et al. 2012).

Generally, illicit drugs can be classifed into one of four major types; stimulants, depressants, narcotics and hallucinogens, and are defined as substances, nonprescribed distribution and use of which is prohibited by law[2] (Houck and Siegel 2010). According to the 2010 '*Global Burden of Disease'* study, the adverse health outcomes of drug use can be determined by two separate pathways; a direct pathway, such as death or morbidities related to drug overdose, and an indirect pathway, through an increased risk of mental healh problems, addicition, injury, suicide, and diseases such as liver failure, hepatitis, cancer, or HIV (Degenhardt et al. 2013, Grant, Lust, and Chamberlain 2019).

Criminalisation of illicit drug possession and/or consumption used to be considered a universal policy instrument to reduce the health and social burden associated with this behaviour. However, prohibition as a policy instrument has faced criticism from legal and public health scholars, sociologists and philosophers alike. Possible negative effects include increased crime, lack of regulation, stigmatization, and potential unwillingness to seek treatment for fear of prosecusion. Alternatives to blanket prohibition include harm-reduction approaches that either aim to prevent the onset of drug use or reduce the frequency of drug use among those who already began using drugs. In general, they fall into the following categories: educational, psychosocial, family, mass media, and community-based treatments. They can be universal or targeted and may be mandated at national, municipal, neighbourhood, or individual levels (National Collaborating Centre for Determinants of Health 2013, Ritter et al. 2005).

[2] A comprehensive list of illicit drugs and their classification can be found in the 2016 report '*Terminology and Information on Drugs'*, published by the United Nations (United Nations Office on Drugs and Crime 2016).

Despite considerable global expenditure on drug use prevention and treatment, the overall burden of problematic use of illicit substances has increased over the last few decades, leading countries such as Canada and the United States to declare the opioid crisis national emergencies (Ritchie and Roser 2018, Spooner and Hetherington 2005).

It has, however, been widely established that the risks associated with drug use are not uniformly distributed across the population. Evidence suggests that certain subpopulations are at higer risk of initiating illicit drug use, as well as developing drug use disorders and suffering from multiple harmful comorbidities (McCabe et al. 2007). Recent research points to significant differences in drug use across a range of sociodemographic characteristics, rendering individuals with intersecting risk factors (e.g. visible minority youth from low-income households) especially vulnerable and susceptible to social stigma or discrimination (Moon et al. 1999). Indeed, non-white ethnicity, low socioeconomic status, low educational attainment, unemployment and young age are the five most well-established and co-occuring risk factors for illicit drug use and reduced odds of recovery in high-income countries (McCabe et al. 2007, Patrick et al. 2012, Haider et al. 2009, DeSimone 2002).

Moreover, alcohol addiction and mental health disorders, such as depression, anxiety, suicidal thoughts, bipolar or post-traumatic stress disorders, are among the most common comorbidities associated with illicit drug use itself, its respective risk factors and underlying pre-conditions, such as trauma (Ritchie and Roser 2018). Due to these co-occuring phenomena, we observe substantial and well-documented social disparities in health outcomes related to drug use and associated comorbidities on a global scale.

PROGRESS-Plus Framework and its relevance to the thesis

In order to address disparities in drug use and apply an equity lens to existing interventions, this thesis will use an adapted version of PROGRESS-Plus, a classification framework developed by Evans and Brown in 2003 and modified by Oliver et al. in 2008 (Evans and Brown 2003, Oliver et al. 2008). The framework was designed to capture common socially stratifying factors responsible for unfair differences in disease burden, notably as a reminder that inequity may arise from categories that reach far beyond socio-economic status (Evans and Brown 2003, O'Neill et al. 2014).

PROGRESS-Plus is an acronym that stands for seven evidence-based, individual-level characteristics established as factors with a strong potential to stratify health outcomes and opportunities;

- **P**lace of residence
- **R**ace/ethnicity/culture/language
- **O**ccupation
- **G**ender/sex
- **R**eligion[3]
- **E**ducation
- **S**ocioeconomic status
- **S**ocial capital
- **+** additional at-risk factors, as identified through relevant research evidence

(Cochrane Collaboration 2021)

PROGRESS-Plus represents a systematic way to define and classify factors attributable to the external environment and other conditions beyond an individual's control. Use of the framework

[3] It is important to note here, that religion is not conceptually equivalent to religiosity, yet the PROGRESS-Plus Framework assumes the meaning of the latter. Religiosity can be understood as a personal attribute with a possible scale of intensity and evaluated as an individual-level characteristic, while the 'religion' is a noun that distinguishes between different types of religions, such as Christianity or Islam. While 'religion' is included as a potential disadvantage factor in the PROGRESS-Plus framework, it is misleading. Firstly, it is crucial to understand 'religion' in the meaning of 'religiosity', or the extent to which one practices a given religion. Secondly, we must appreciate that when it comes to health behaviors and drug use, evidence suggests that religiosity may be a protective factor rather than a disadvanage factor, as could be the case of the 7th day adventists, who attach considerable importance to healthy lifestyle, including proper diet, exercise and discourage alcohol or drug use (Dudley, Mutch, and Cruise 1987).

was recommended by the Campbell and Cochrane Equity Methods Group within the PRISMA-Equity 2012 extention of reporting guidelines for the best practice in health equity-oriented knowledge syntheses (Welch et al. 2012). According to O'Neil and colleagues, "*each PROGRESS factor can be justified on the basis of unfair differences in disease burden and an intervention that can effectively address these health inequities*" (O'Neill et al. 2014). They assessed the utility of the framework to guide conceptualization of disadvantage in 11 systematic reviews and argued for its inclusion in new systematic reviews examining effectiveness of health programs, evaluation of interventions, and identification of barriers to their successful implementation among disadvantaged groups.

This is particularly relevant for the purposes of Manuscript 1, as presented in Chapter 2 of this thesis, because its aim is to explore and map the extent to which different at-risk subgroups are represented in systematic evaluations of illicit drug interventions. PROGRESS-Plus includes characteristics of all major subgroups at risk of illicit drug use, as identified in the previous section, and will be useful to determine which subgroups are sufficiently represented in systematic reviews evaluating drug use interventions in a focused and measurable way.

Table 1 below outlines relevant PROGRESS-Plus disadvantage factors with my definitions based on a brief literature review, adapted in the context of inequitable societal distribution of illicit drug use and help-seeking behavior. In my conceptualization of the framework, I made minor changes to the original framework terminology. Particularly, I expanded gender as a PROGRESS-Plus factor beyond the binary male/female classification, to include non-binary gender status, as well as sexual orientation. While the patterns, trends and distributions of illicit drug use may substantially differ across different genders and sexual orientations, each may represent similar underlying identity factors associated with increased risk of drug use. I also expanded Disability as a Plus factor into 'Disabilities and Comorbidities', inclusive of both mental and physical disabilities and diseases. In the original expanded framework, disability was used to encompass both concepts, despite conceptual differences. Lastly, I chose to replace 'other vulnerable groups' as a Plus factor with 'time-dependent life events', because I believe this phrasing is better able to capture the importance of transitionary life periods, major events, and disadvantaged positions within a society.

Table 1: PROGRESS-Plus Factors and their individual relevance to illicit drug use

PROGRESS-Plus Factor	Definition in the context of illicit drug use
Place of residence	Residence in a disadvantaged area with potentially limited access to care (i.e., rural areas), high crime rates and drug availability (i.e., inner city urban areas), or homelessness may all negatively affect individuals' ability to resist drugs and seek help for misuse (Rhew, Hawkins, and Oesterle 2011, Mack 2017, Tyler, Kort-Butler, and Swendener 2014).
Race/ethnicity/ culture	Ethnic, racial, and cultural minorities or individuals who commonly speak a non-dominant language in their region of residence (i.e., individuals with African American, Hispanic, or Indigenous origins), may face discrimination and additional challenges related to illicit drug use and/or access to health and social services compared to their Caucasian counterparts (Newcomb et al. 2014, Delahunty and Putt 2006).
Occupation	Under-employment, unstable employment, work in unsafe conditions and joblessness, as well as a lack of employee benefits, insurance plans and other undesirable working conditions may negatively affect individuals' ability to resist drugs, seek help for substance use and recover (Henkel 2011, MacDonald and Pudney 2000).
Gender/sexual orientation	Gender self-identification and non-heterosexual orientation may affect individuals' perception of support available, exposure to violence, discrimination, drugs, and stigma associated with illicit drug use and help seeking (Newcomb et al. 2014, Schuler, Stein, and Collins 2019).
Religion	Religiosity (see Footnote 3 above) is commonly described as a protective factor against substance use in existing literature, affecting individual's perception of, and resilience to initiating illicit drug use (Dudley, Mutch, and Cruise 1987, Engs and Mullen 1999). Due to evidence suggesting this predominantly protective nature of religiosity when it comes to illicit drug use outcomes, we will omit religion as a disadvantage factor for drug use from our analyses.
Education	Individuals with low educational achievement level (i.e., high school degree or lower) may be less likely to benefit from existing interventions than their more educated peers. Low educational achievement is also a multifaceted disadvantage factor associated with a high probability of co-occurring occupational disadvantage, low socio-economic status, and residence in a disadvantaged area; all strongly associated with an increased risk of drug use and inability to access necessary help (Chatterji 2006).
Socioeconomic status	Low socioeconomic status, commonly co-occurring with low education level, residence in a disadvantaged area, and occupational instability can affect the ability of individuals to access and/or afford health promoting resources and render them more vulnerable to harmful drug use than their wealthier counterparts (Gerra et al. 2020).
Social capital	Low social capital (i.e., insufficient community network, family relationships and loneliness) may affect the availability of social support and resilience to drugs. Insufficient social network may render individuals more vulnerable to peer pressure and may significantly affect successful recovery after drug use initiation (Åslund and Nilsson 2013).

+ Plus 1: Age	Teenagers and young adults may be significantly more vulnerable to drug use initiation and peer pressure than other age groups, more likely to find access to and experiment with illicit drugs (Lynskey et al. 1999). Similarly, research evidence suggests that children and young persons may have less impulsivity control than older individuals, due to incomplete brain development (de Wit 2009).
+ Plus 2: Disabilities and Comorbidities	Disabilities, such as mental health disorders, chronic pain, diabetes, learning difficulties and physical handicaps among other things may significantly affect quality and self-perceived value of life. These comorbidities may contribute to increased risk of illicit drug use as a coping mechanism, while at the same time, drug use may lead to increased risk of developing further comorbidities, such as depression, chronic pain, or disabilities. They may also render individuals less likely to be able to access and benefit from available help (i.e., non-braille mass media interventions may be unsuitable for blind individuals) (Moore and Li 1998, Tyler et al. 2014).
+ PLUS 3: Substance abuse disorders	Individuals with existing substance abuse disorders, such as alcohol, cigarette, or soft-drug (i.e., cannabis) addictions may be more susceptible to initiate heavy drugs and develop addictions to them. They may also suffer from additional comorbidities associated with existing substance use addictions, such as depression(Carpenter, McClellan, and Rees 2017).
+ PLUS 4: Time-dependent life events	Other at-risk subgroups include individuals experiencing important life transitions, such as released and incarcerated criminal offenders, who may have history of drug abuse or violence and face societal stigma, discrimination, and inability to find suitable employment. They may likewise not possess the same ability to access resources than their counterparts without a criminal record. Additional groups facing disproportionate challenges are, for example, co-abusing partners and individuals living with or next to drug abusing relatives and roommates. These individuals have increased access to drugs and risk of peer pressure (Cavacuiti 2004, Mumola and Karberg 2006).

First and foremost, it is crucial that we grasp and address the structural reasons behind these observed PROGRESS-Plus disadvantage factors. However, finding and implementing effective solutions to address large scale social issues, such as structural unemployment, racial discrimination or growing inequalities in wealth, educational attainment, and social status, all strongly associated with risk of illicit drug use, may take a long time, and prove politically difficult. It is, therefore, necessary to complement our societal efforts to address the roots of these disadvantage factors with more downstream, demonstrably effective interventions.

In designing interventions aimed at illicit drug use and associated comorbidities, equity-minded decision-makers need to consider the vast potential of different PROGRESS-Plus dimensions of disadvantage (Table 1) that affect both risk of harmful drug consumption and the extent to which individuals can benefit from the prevention and treatment interventions available to them.

Illicit drug use, subpopulations, and the COVID-19 pandemic

The uncertainty, fear and isolation associated with the pandemic and the lockdown measures implemented worldwide to help curb the spread of COVID-19, have taken a serious toll on the wellbeing, mental and physical health of most people. Evidence of the large-scale impact of the COVID-19 pandemic beyond the direct clinical effects of the SARS-COV-2 virus is now emerging.

Over the course of the COVID-19 pandemic, many of the identified disadvantage factors have been exacerbated. Mental health disorders and unemployment have become more prevalent (Xiong et al. 2020), anti-Asian sentiment and stigma have grown (Nguyen et al. 2020), educational disruptions were widespread (d'Orville 2020), and distancing requirements limited ability to engage in meaningful social interactions. Similarly, homeless individuals and those living in disadvantaged areas may have been disproportionately affected by the pandemic both directly (i.e., through higher number of incident cases of COVID-19) and indirectly (i.e., through prolonged exposure to environmental stressors and health risks associated with disadvantaged living conditions) (Samuels-Kalow et al. 2021).

Such increased disadvantages often concentrate within specific subpopulations experiencing multiple risk factors. These subpopulations are not only vulnerable to increased risk of COVID-19 infection and significantly worse disease progression but may also face additional burdens associated with mental exhaustion, occupational hazard, inability to protect family members and afford treatment in case of infection. Facing such stressors may render the subpopulations with multiple PROGRESS-Plus disadvantage factors at higher risk of initiating or increasing illicit drug consumption as a coping mechanism.

When it comes to illicit drug use as a global health issue, health experts have raised substantial concerns about social isolation and stress during the COVID-19 pandemic (McKay and Asmundson 2020). Moreover, services targeted at harmful drug use of subpopulations at-risk, such as safe injection sites, have reduced their operating capacity, or closed altogether during the pandemic, contributing to a further gap in disadvantage within our societies (Roxburgh et al. 2021).

While current evidence of changes in illicit drug use patterns during the COVID-19 pandemic is limited, we found studies that establish preliminary patterns of change among some PROGRESS-Plus domains compared to pre-pandemic times. For example, Horigian and colleagues found that low social capital and loneliness among young people during the pandemic is associated with increased illicit drug use (Horigian, Schmidt, and Feaster 2021). Similarly, Panchal and colleagues found that during the pandemic, people with existing mental health and substance abuse disorders increased problematic substance use and faced additional barriers to the availability of public resources and access to needed help (Panchal and Kamal 2021).

Results from a recent study of illicit drug use among gender and sexual orientation minorities during the pandemic show that, while the overall prevalence of non-cannabis drug use decreased, the frequency of use increased (Janulis, Newcomb, and Mustanski 2021). Another study reported similar trends of decreased prevalence, but increased frequency of substance use among adolescents in Canada after implementation of social distancing rules (Dumas, Ellis, and Litt 2020). These findings highlight the potential decrease in access to illicit substances and opportunities to socialize with peers among subpopulations at-risk, but a co-occurring increase in the risk of misuse and abuse among a subgroup of users associated with a higher burden of stress and disadvantage during the pandemic.

Chapter Summary

First, I provided a literature review of the current debate on policy design types and their relation to the distribution of health outcomes across the population. This section offered important context for the manuscripts that follow, because it allowed me to conceptualize existing policy frameworks relevant for evaluation of illicit drug interventions.

Second, I presented an overview of research on the specific distribution of population-level illicit drug use and found persistent socio-demographic disparities in illicit drug-related health outcomes on a global scale. The manuscripts included in my thesis draw from this body of evidence, for the section provides a strong rationale for both conducting the studies in the first place and identifying an equity framework that aims to capture the existing domains of disadvantage, such as the PROGRESS-Plus Framework, also outlined in this chapter.

Lastly, I reviewed the current state of research evidence for the impact of the COVID-19 pandemic on existing distribution of illicit drug use and disadvantage across the previously identified PROGRESS-Plus subpopulations at-risk. The findings point to an overall increase in drug use, as well as emerging evidence for a disproportional burden of this increase among certain subpopulations. Such evidence provides an important background and context for Manuscript 2.

Chapter 3: Manuscript 1

Preface

This manuscript is an umbrella review of systematic reviews exploring the effectiveness of illicit drug interventions for individuals with PROGRESS-Plus characteristics. In it, we explore the extent to which specific subpopulations susceptible to disproportional illicit drug use burden are included in high-quality research evaluating illicit drug use policy interventions. We sought to identify policy types that appear to be effective for specific subpopulations and identify potential gaps in and quality of evidence base for different PROGRESS-Plus domains. This manuscript is in preparation for submission to *Addiction*.

How are PROGRESS-Plus subpopulations represented in systematic reviews evaluating illicit drug policy interventions? A review of reviews

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MB was responsible for the concept, design, and main analysis of this study, as well as the written draft of the manuscript. MB, KC and DY were involved the study selection, data extraction and quality appraisal of included studies. AQV and AK provided feedback on the concept and design of the study as well as critical revisions for important intellectual content. All authors contributed to the revisions to the study as well as read and approved the final manuscript.

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Conflicts of interest
The authors declare that they have no conflicts of interest relevant to the content of this article.

Availability of data and material
All data, inclusive of the full ENDNOTE X9 search file, data extraction and quality appraisal documents, are available upon request.

Ethics approval
Not applicable

Consent to participate and publish
Not applicable

Abstract:

Background and Aims: Current evidence suggests that certain subpopulations bear a disproportional burden of illicit drug use and related comorbidities. With drug use being a risk factor for many chronic and acute diseases, addressing such an important health determinant could reduce health disparities prior to their clinical manifestation. This paper uses umbrella review methodology to assess the representation of PROGRESS-Plus Equity Framework subpopulations in systematic reviews evaluating illicit drug interventions. It further aims to identify intervention characteristics associated with effective policy design for individuals experiencing structural PROGRESS-Plus disadvantage factors.

Methods: Three databases were systematically searched for systematic reviews and meta-analyses. The data was double extracted, and quality was assessed using AMSTAR 2. The results were synthesized narratively for each relevant PROGRESS-Plus domain.

Results: Fifty-three studies were included in the review, of which 28 evaluated drug interventions for one PROGRESS-Plus characteristic and 25 looked at intervention effectiveness for multiple co-occurring domains. The most represented domain was age (adolescents or young adults under 25), place of residence (rural/inner city/vulnerably housed population) and race, ethnicity, or culture (racial/indigenous minorities). We found some evidence of effectiveness of targeted policies, especially for ethnic minorities, who may not benefit proportionately from universal interventions alone. No research syntheses evaluated drug policies for four PROGRESS-Plus domains, including occupation, low social capital, and disability.

Conclusions: Our findings point equity-concerned decision makers towards targeted universalism when designing interventions, and to consider supplementing universal interventions with program adaptations for minority sub-populations. In this review, we identified the following subgroups as under-represented in existing knowledge syntheses: religious minorities, individuals with disabilities, low educational attainment, socially isolated and unemployed individuals. Further research is needed to fill this subgroup-specific gap in knowledge syntheses. This is pertinent to ensure that decision-makers interested in using the best available evidence consider how their decisions affect all relevant stakeholders.

Keywords: Health Equity, Drug Use, Policy Intervention, High-Income, Public Health, Targeted Universalism, Umbrella review

Trial Registration: The umbrella review protocol was prospectively registered with PROSPERO (CRD42021251045)

Introduction

The argument that public policy design affects the distribution of population health and health inequities has long been recognized and supported by a wide base of research evidence (Arblaster et al. 1996, Naik et al. 2019). Over the last decades, research production and publication on the effects of policy interventions on health-related outcomes grew rapidly. At the same time, we saw an increased use of systematic review and meta-analysis methodology from health-sciences in sociology and social epidemiology. This has been an important step towards meeting the goals set by the World Health Organization (WHO) Commission on Social Determinants of Health (CSDH) and actively addressing health inequities, because availability of rigorous, extensive, and high-quality evaluations of health policy effectiveness, such as those offered by well-conducted systematic review, are essential to address health inequities. For this purpose, however, it is crucial to move beyond evaluating interventions based on their average effects on health and towards addressing intervention impact with respect to different population subgroups. This is because not all relevant stakeholders may benefit equally from the interventions available and using mean policy effects may mask the potential of these policies to perpetuate or even increase existing health inequities.

This potential problem with policy evaluations is especially pressing in the broader context of illicit drug use and substance use disorders (SUD), which, as recent research suggests, are unequally distributed across socio-economic groups, genders, or ethnicities, and, at the same time, prone to differential intervention effectiveness across these population subgroups (Patrick et al. 2012, NIDA 2020b, McCabe et al. 2007, Cao, Burton, and Liu 2018). With illicit drug use being a major adjustable risk factor for many chronic and acute diseases, addressing how well different drug policies work for subpopulations could help us reduce social inequalities in health outcomes related to drug use before the disease onset becomes a critical issue both in itself and as a health equity concern (National Center for Health Statistics (U.S.) 2012, Pampel, Krueger, and Denney 2010, Petrovic et al. 2018). The importance of not only preventing illicit drug use overall, but also understanding whether and how specific policies work for different disadvantaged minority groups, is especially pressing considering that preventable disparities in health outcomes constitute a serious ethical, social, and political concern. To effectively address this complex issue, it is crucial to provide decision-makers with well-conducted systematic reviews that evaluate illicit

drug policy effectiveness with respect to different subpopulations deemed at-risk. Such knowledge syntheses represent the best available evidence to equity-concerned decision makers.

We were unable to identify a comprehensive overview of existing systematic reviews on effectiveness of illicit drug interventions among different subpopulation at risk. Given the importance of systematic reviews in informing evidence-based decision-makers and the existing evidence pointing to a non-uniform intervention effectiveness among different population subgroups, it is critically important to understand if these subpopulations at-risk included in systematic reviews in order to address persistent health inequalities.

This umbrella review aims to provide a comprehensive synthesis of the existing systematic reviews of illicit drug intervention effectiveness among different subpopulations at elevated risk of harmful illicit drug use and differential intervention effectiveness. By embedding the PROGRESS-Plus classification framework for common disadvantage factors within the umbrella review, we have adopted a novel, adaptable, and accountable methodological way of assessing whether relevant stakeholders at-risk are included in impactful systematic reviews, which could be used within any policy evaluation field.

Research Objective

The main objective of the study is to synthesize and classify the existing knowledge of the effectiveness of illicit drug policy interventions among relevant PROGRESS-Plus population subgroups from high-income countries OECD and non-OECD EU-28 countries.

Methods.

This paper used umbrella review methodology to synthesize evidence from peer-reviewed systematic reviews. The protocol for this review was developed prior to the search and registered with PROSPERO (CRD42021251045) in January 2021. As per the standard practice in evidence-based syntheses, inclusion criteria were defined a priori in terms of the ‘Population, Intervention, Comparison, Outcome and Study Design (PICOS) format (Higgins and Thomas 2021). For full inclusion and exclusion criteria, see Table 1 below.

Table 1: PICOS inclusion and exclusion criteria

Study Characteristics	**Inclusion Criteria**
Population	Individuals of any age from any high-income OECD country or non-OECD EU-28 country that can be categorized as members of one or more PROGRESS-Plus disadvantage groups. If a review included individuals from all countries, it will only be included if relevant data could be extracted for individuals from high-income countries.
Intervention	Any policy intervention, universal or targeted, at national, municipal, neighbourhood or individual level mandated or funded by local, national, or international governmental organizations, regardless of who delivers them. A universal intervention is defined as a service provided to the whole population within a given jurisdiction, regardless of individual characteristics. Targeted interventions, on the other hand, are provided to selected individuals based on their specific characteristic, such as a geographic location, minority subpopulation membership or employment status.
Comparison	Systematic reviews or meta-analyses that include uncontrolled studies or studies with a reference group that received an alternative policy intervention, standard treatment, or no intervention; the reference group could either be from the same jurisdiction at a different time or a different jurisdiction. Reference group could either be drawn from the same PROGRESS-Plus domain or general population.
Outcome	Effects inclusive of (but not limited to) differences in the prevalence, incidence, mortality, morbidity, accidents, and injuries associated with illicit drug use.
Study Design	Peer-reviewed reviews, inclusive of systematic reviews, scoping reviews, meta-analyses, and umbrella reviews published in English. Following the practice of previous umbrella reviews in the field, publications had to meet two compulsory Database of Abstracts of Reviews of Effects (DARE) criteria; a defined review question with at least two of; the participants, interventions, outcomes or study design and a search strategy with at least one named database, in conjunction with either reference checking, hand-searching, citation searching or contact with authors in the field (Bambra et al. 2009, Hillier-Brown et al. 2019, Main et al. 2008). Reviews of primary studies with the following study designs: randomized and nonrandomized controlled trials, cluster trials; prospective and retrospective cohort studies, cross-sectional studies (with or without control groups) and studies using interrupted time series design.

Exclusion Criteria	**Justifications**
Reviews that include primary studies using modelling and simulation design.	Such studies do not represent the same type of evidence as observational studies and therefore cannot be reliably synthesized with observational intervention implementation studies
Reviews that exclusively focus on tobacco and alcohol-related outcomes	Analysis of tobacco and alcohol-related outcomes will be covered by two additional reviews conducted by the same research group.
Reviews exclusively conducted in low- and middle-income countries.	Due to variation in resources in low- and middle-income countries compared to high-income countries, results from both country groups cannot be synthesized together. A separate synthesis is required for effective policy recommendations to each setting.
Reviews that focus solely on primary care, pharmacological and therapeutic interventions in a medical setting	This review is specifically focused on social or public policy-level interventions in a non-medical setting.

To capture the effectiveness of policies on drug use among different subpopulations, we have chosen to use an adapted PROGRESS-Plus equity framework to classify our populations of interest into minority subgroups based on their membership in at least 1 PROGRESS-Plus domain identified as a disadvantage factor for illicit drug use. This framework allowed us to apply an equity lens to interventions and to identify characteristics that stratify health opportunities or outcomes (O'Neill et al. 2014). The adaptations to the framework were made by the study authors to reflect the relevance of each PROGRESS factor to the study of illicit drug use. Table 2 presents a list of the domains included the framework with examples for each domain. A more comprehensive literature review relating each domain to subpopulation-specific illicit drug use research is included in Appendix A.

Table 2: Description of adapted PROGRESS-Plus disadvantage domains

PROGRESS-Plus Factor	**Disadvantage description**
Place of residence	i.e., Rural areas, inner city urban areas, vulnerable housing, and homelessness
Race/ethnicity/culture	i.e., Ethnic, racial, and cultural minorities, indigenous population
Occupation	i.e., Unstable, unsafe employment, unemployment, lack of employee benefits
Gender/sexuality	i.e., Gender self-identification, non-heterosexual orientation
Religion[4]	N/A
Education	i.e., Low educational achievement level
Socioeconomic status	i.e., Low socioeconomic status
Social capital	i.e., Loneliness, insufficient community network, social support
+ Plus 1: Age	i.e., Youth population under the age of 25
+ Plus 2: Disabilities and Comorbidities	i.e., Mental health disorders, chronic pain, diabetes, learning difficulties, physical handicaps
+ Plus 3: SUD	i.e., Individuals with alcohol, cigarette, and drug addictions, i.e., substance use disorders (SUD), people who inject drugs (PWID)
+ Plus 4: Time-dependent life events	i.e., Released, and incarcerated criminal offenders, co-abusing partners, individuals living with or next to drug abusing relatives and roommates.

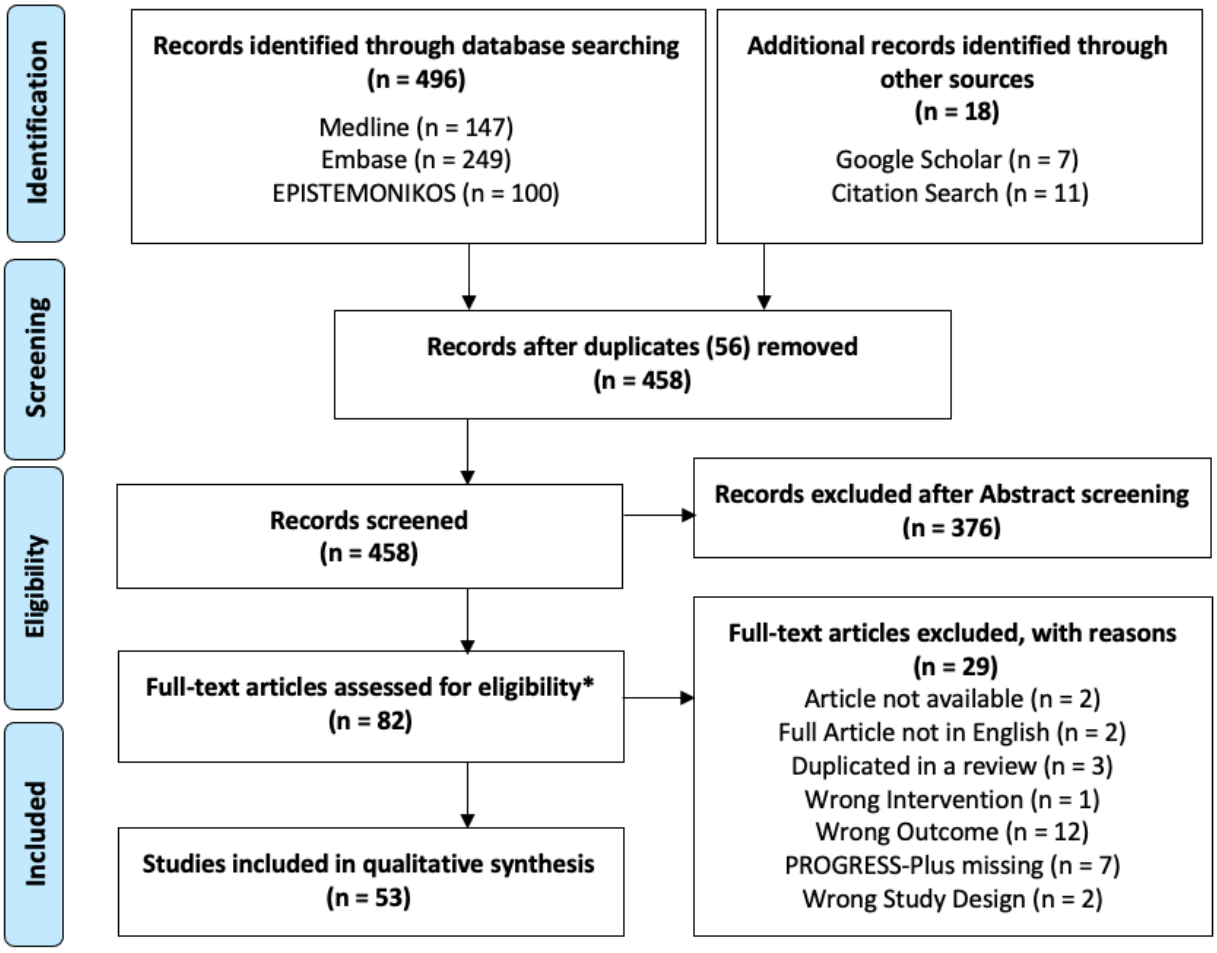
Search strategy

A literature search strategy for existing systematic reviews was developed by the first author and peer-reviewed by a liaison librarian, Genevieve Gore. Three databases were searched (with host sites in parentheses): MEDLINE (Ovid), EMBASE (Ovid) and EPISTEMONIKOS. The searches were conducted without time frame restrictions and selected references were imported into

[4] Research evidence suggests that religiosity is a protective factor for illicit drug use and so it will be excluded from the Framework as a disadvantage factor.

ENDNOTE X9. Key words searched were adapted to each database host site. A grey literature search was conducted by citation follow-up from included studies as well as through a Google Scholar search by the first author. (see Appendix B for full search strategy including detailed search terms). The screening process at title/abstract level was double extracted by two independent reviewers. Conflicts was resolved by discussion. There was a high agreement in both parts of the screening (abstract: 85.4% and full text: 87.9%). A precautionary approach was used to include studies unless exclusion was clearly justified by the exclusion criteria listed in Table 1. A kappa statistic was not calculated, for in cases of a relatively low inclusion rate compared to the number of papers found, the score is not appropriate (Naik et al. 2019). Full text review, data extraction and quality appraisal were conducted independently by two authors. Figure 1 below shows a PRISMA flow chart of the distinct phases of this umbrella review.

Figure 1: PRISMA Flow Chart



Data synthesis and quality appraisal

Data extraction was conducted by filling out an adapted version of the Data Collection Form template for randomized controlled trials (RCT) and non-RCT from the Cochrane Collaboration (Cochrane Collaboration 2020). Where not all findings of the included reviews were relevant to the scope of our umbrella review, only relevant findings were extracted. Given the heterogeneous methodologies of included reviews, the summary effect estimates reported in our review were handled accordingly:

1. ***For narrative reviews*:** '*positive*' or '*negative*' intervention effect was based on whether the authors of the systematic review reported that the majority of individual studies included in the review reached a similar conclusion about intervention effectiveness on illicit drug use or related comorbidities. We reported an '*inconclusive*' summary effect estimate if the individual studies in the review presented findings that were imprecise, or insignificant. A 'no' effect size was reported when the majority of included studies reported no effect of the intervention studied on relevant health outcomes and a '*mixed*' effect was reported when individual studies in the review came to conflicting conclusions about the effectiveness of the intervention studied.

2. ***For meta-analyses*:** '*positive*' or '*negative*' intervention effect was based on whether the meta-analysis reported a clear positive or negative summary result from a statistical synthesis of individual studies. We reported an '*inconclusive*' summary effect estimate if the statistical synthesis did not reveal a clear trend in intervention effectiveness across included studies (i.e., the overall estimate was imprecise or insignificant). '*No*' effect size was reported when the meta-analysis reported a null overall estimate for intervention effectiveness and a '*mixed*' effect was reported based on forest plots (when applicable), where individual studies reported conflicting and statistically significant conclusions.

As part of the data extraction, each review included was assessed against all 16 components of AMSTAR 2, a critical appraisal tool for systematic reviews of randomized and non-randomized studies and meta-analyses (Shea et al. 2017). The components included questions related to the quality of the search strategy, research conduct, heterogeneity, conflicts of interest and risk of bias assessment, such as selection bias or publication bias. We have chosen to judge studies as either of high, moderate or low risk of bias based on the percentage of 'applicable' AMSTAR 2

components answered as 'Yes' (see Table 3 for details). The condition was phrased as 'appropriate' as opposed to 'all' AMSTAR 2 components, because some questions specifically target bias assessment associated with the statistical methodology of meta-analyses, which were not applicable to some narrative systematic reviews and umbrella reviews included. Scoping reviews were assessed for quality in the same way as systematic reviews, using AMSTAR 2. However, in the case of scoping reviews, questions related to the quality of reporting as well as risk of bias were not considered, for they are not necessary components of a scoping review methodology. While all 16 components were relevant to meta-analyses, only 12 were used to assess narrative systematic reviews and 10 for scoping reviews.

Table 3: AMSTAR 2 Assessment

AMSTAR 2 Quality Assessment	Percentage (%) of AMSTAR 2 questions evaluated as YES
Low risk of bias	>80% of the appropriate questions answered as YES
Moderate risk of bias	80-50% of the appropriate questions answered as YES
High risk of bias	<50% of the appropriate questions answered as YES

The findings were presented both in a tabular form for each PROGRESS-Plus disadvantage factor and summarized through a narrative synthesis. A quantitative data synthesis, such as a meta-analysis was not conducted as part of this review, due to the heterogeneity of included populations and interventions.

Results

Description of included reviews:

We identified a total of 53 eligible reviews of illicit drug interventions effectiveness with health effect evaluation for individuals experiencing at least one relevant PROGRESS-Plus disadvantage factor (see Figure 2)[5].

Twenty-seven of these studies evaluated the interventions for individuals experiencing one single PROGRESS-Plus disadvantage factor. Of these, the most represented PROGRESS-Plus subpopulations in reviews were youth population (6/27), racial or ethnic minority population

[5] The reviews included in this paper covered a total of 2425 primary studies, 1211 of which were relevant for this review given our specified population subgroups, setting and outcome of interest. Since some reviews eligible for inclusion in our study included ineligible primary studies based on our inclusion criteria (i.e., studies of general population without subgroup analyses or studies in LMIC setting), results from these primary studies were excluded.

(5/27), substance use disorders (5/27) and disadvantaged place of residence (4/27). Effectiveness of drug interventions for individuals experiencing multiple co-occurring PROGRESS-Plus factors was examined in 26 reviews. Most of these reviews (19/26) concentrated on age, namely children, adolescents, or specific vulnerable adults such as women of childbearing age, experiencing at least one additional PROGRESS-Plus disadvantage factor, such as vulnerable housing, ethnic or sexual minority status.

Figure 2: Number of papers by inclusion of PROGRESS-Plus factors

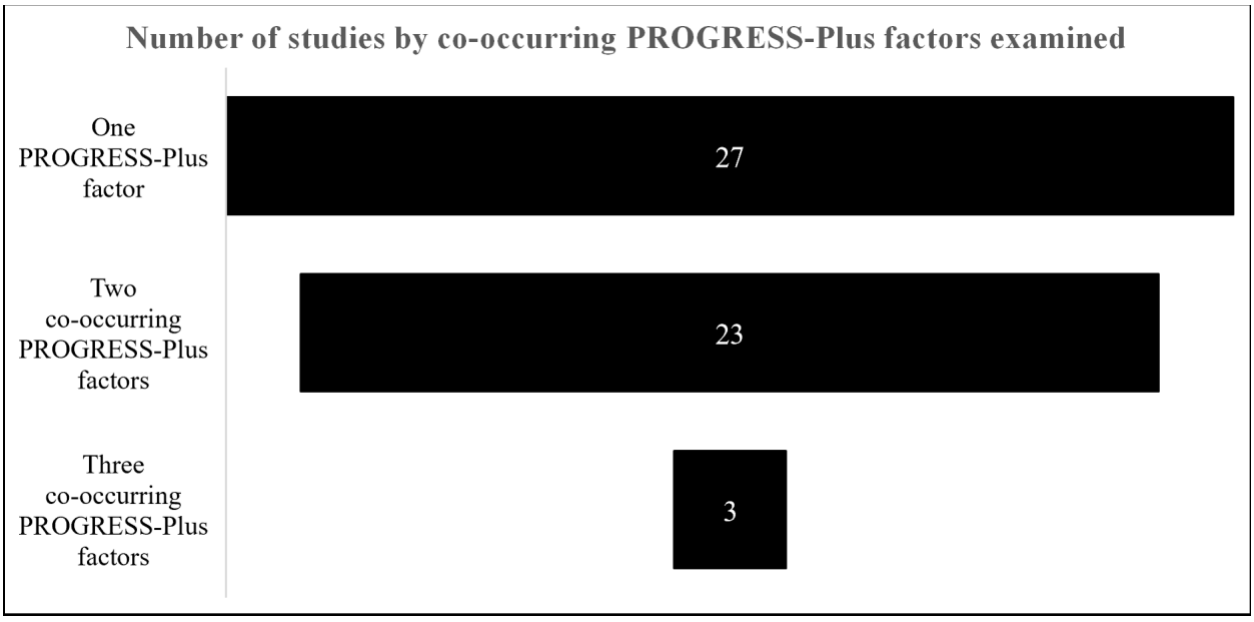
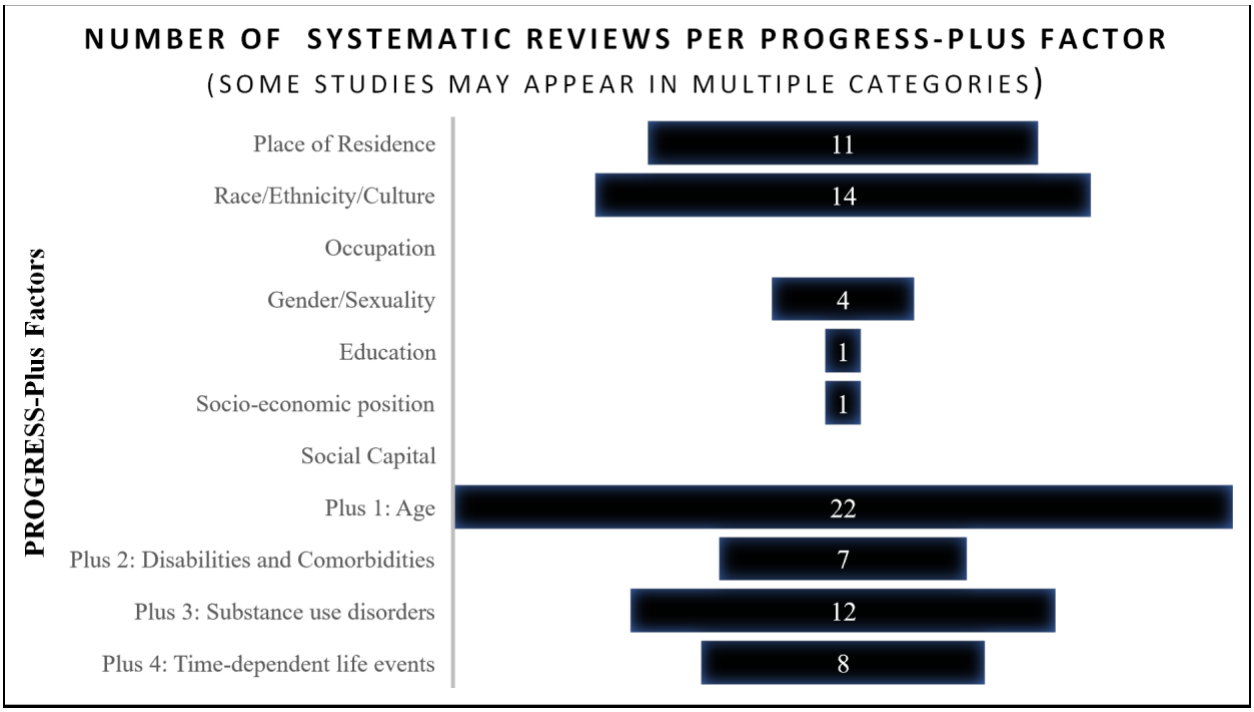


Figure 3 below shows the number of reviews that explicitly evaluated illicit drug policies for each PROGRESS-Plus disadvantage subgroups. Reviews that evaluated policies for multiple co-occurring PROGRESS-Plus factors were enumerated in all respective categories and therefore, the sum of all reviews on Figure 3 is higher than the 53 included reviews.

None of the included reviews looked at the effectiveness of illicit drug policy interventions for individuals with a vulnerable occupational status, low social capital, and religious minorities. Interventions for individuals with low educational attainment and socio-economic status were evaluated in only one respective review. Age, and specifically youth population, such as children, adolescents, and emerging adults, was the most represented population subgroup for which illicit drug interventions were evaluated (24/53), followed by racial, ethnic, and cultural minorities

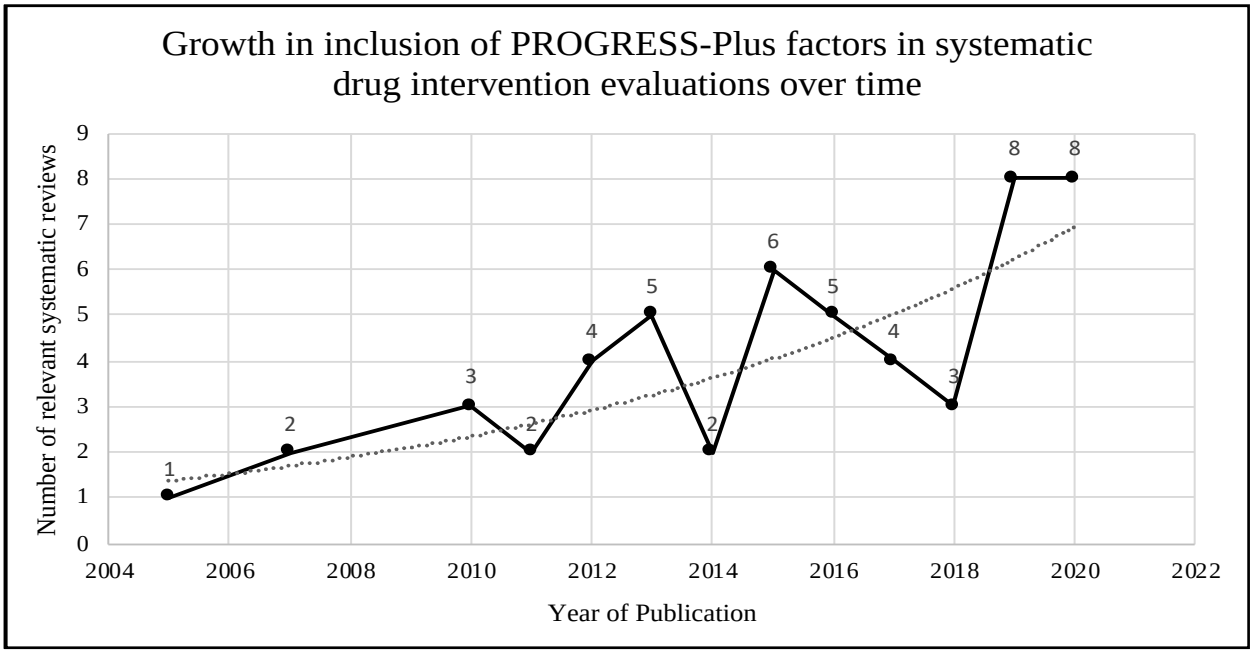
(14/53), individuals with existing substance use disorders (12/53) and individuals living in a disadvantaged place of residence (11/53).

Figure 3: Number of systematic reviews per each PROGRESS-Plus domain



Despite no time restrictions, all the reviews included in this paper were published after 2005 (see Figure 4 below for a publication date timeline for included studies). Most of the included reviews were published within the last 10 years, pointing to an increasing awareness of the value of systematic reviews, advances in conducting them and potentially a growing interest in subgroup policy evaluation analysis after the publication of The Marmot Review in 2010. Most of the reviews were set exclusively in the United States (25/53), either by design or because only US primary studies were identified in the reviews. Of the additional 28 reviews, 23 explicitly focused on OECD high-income countries and 5 were without a specific country development setting, but only included high-income OECD countries. Within these reviews, most primary studies were conducted in the United States.

Figure 4: Number of papers including PROGRESS-Plus domains in systematic drug evaluations over time



Of the included studies, 20 reviews were assessed as being at low risk of bias, 19 as being at moderate and 14 at high risk of bias using the AMSTAR 2 quality assessment tool for systematic reviews and meta-analyses. Approximately 58% of the included reviews used exclusively a systematic review methodology (31/53), 15% provided both a systematic review and a meta-analysis (8/53), and an additional 12% used a meta-analysis methodology only (7/53). We also included 3 well-conducted scoping reviews and 4 umbrella reviews that explicitly reported relevant outcomes (7/53). Most reviews included primary studies that compared the effectiveness of their intervention of interest either against no intervention, or standard treatment, using observational study design or randomized control trial design.

Excluded reviews

We have excluded 443 reviews that did not meet our inclusion criteria (see also Figure 1 for a PRISMA flow chart). Most reviews (376) were excluded during the title/abstract screening process. Of the 82 reviews included in the full-text review, 29 were excluded (for exclusion reasons for these reviews, see Appendix C). Most of these reviews were rejected either because the reviews did not include a separate and quantifiable illicit drug use outcome (12), or because the outcome was not evaluated specifically for one of the PROGRESS-Plus disadvantage domains (7).

Effects of illicit drug interventions on PROGRESS-Plus subpopulations

Place of residence

Eleven reviews assessed the effectiveness of illicit drug policy interventions for vulnerably housed or homeless individuals, inner-city and rural dwellers. Of these, four reviews looked at place of residence as the sole domain of disadvantage, and seven stratified the subpopulation further, such as by concentrating on street-connected children (Coren et al., 2016), homeless individuals with existing substance use disorders (Miler et al. 2020, Hwang et al. 2005), or PWID and children in rural areas (Paquette & Pollini, 2018, Hendricks Brown et al. 2007).

Reviews focused on homeless and street-connected individuals either evaluated the effectiveness of universal interventions, such as the provision of supervised injection sites, shelters, and clean syringe access in reducing illicit drug use frequency, or targeted interventions, such as peer support for people experiencing homelessness and case management interventions. Among these interventions, supervised injection sites showed a consistently positive effect across reviews on both drug reduction and associated risk of HIV transmission for homeless and vulnerably housed individuals (Miler et al. 2020). Case management or reintegration interventions were either of mixed or inconclusive effectiveness for the homeless (Ponka et al. 2020, de Vet et al., 2013, Formosa et al. 2021, Coren et al., 2016). Peer support provision from people with past lived experience appeared effective at reducing drug use among the homeless (Miler et al. 2020).

Three reviews focused on intervention evaluation for rural dwellers. One looked at universal public health interventions in a community-setting and found no effect on drug use among individuals living in rural areas and inner-city areas. Another looked at the effectiveness of universal syringe exchange program, clean syringe access and HIV testing for PWID in non-urban pharmacies and found significant geographical barriers to access and worse illicit drug risk outcomes compared to urban dwellers (Paquette & Pollini, 2018). Same authors also found that partner notification programs for rural PWID who tested positive for HIV were effective in curbing HIV transmission. The last review for rural dwellers focused on universal school-based drug prevention programs for children in rural areas, and found positive overall effects on drug use (Hendricks Brown et al. 2007).

Race/Ethnicity/Culture

Overall, 14 reviews evaluated effectiveness of interventions for individuals of different ethnic, racial, or cultural minorities, such as African American, Latino, or Indigenous subpopulations. Five reviews focused on race, ethnicity, and culture as the sole disadvantage factor. The remaining 9 reviews attempted to combine ethnicity with additional co-occurring domains of disadvantage, such as gender (Valdez et al. 2018, Hai, Hammock, and Velasquez 2019), young age (Edwards et al., 2010, Mewton et al. 2018), or mental health and SUD co-morbidities (Guerrero et al., 2013, Leske et al. 2016).

Among the five reviews evaluating interventions for Indigenous subpopulations, most concentrated on targeted, culturally grounded, and deep structure prevention interventions that avoid the separation of mind and body, involving elements, such as language-adapted circle conversations, prayers and dancing in school, family and/or community setting (Snijder et al., 2020, Edwards et al., 2010, Liddell and Burnette 2017). The reviews found mostly positive, but some inconclusive evidence of effectiveness for culturally grounded interventions for Indigenous communities. Targeted behavioral counselling interventions, such as perinatal home visits to pregnant Native American youth, showed mixed effectiveness (O'Connor et al., 2020). Only three reviews looked at how effective universal public health drug prevention interventions with no cultural adaptations are for Indigenous people. Two found inconclusive evidence of effectiveness (Leske et al. 2016, O'Connor et al., 2020), while the third reported an increase in drug use following a multicultural universal prevention intervention in Indigenous communities (Liddell and Burnette 2017).

Latino and African American subpopulations appeared to have a similar, positive response to targeted interventions involving cultural and/or language adaptations (Lauricella et al., 2016). They were also especially effective for ethnic minority individuals with existing mental illnesses and SUD (Guerrero et al., 2013). Similarly, in terms of drug use prevention, ethnic youth appear to respond well to large-scale universal community- and school-based interventions that involve peer-support training (Mewton et al., 2018, O'Mara-Eves et al. 2015), but some reviews found inconclusive effectiveness of universal school-based interventions delivered through external consultants (Gorin et al., 2012). Both universal and targeted interventions aimed at preventing HIV

and drug use among PWID, such as public health prevention programs and language-adapted referrals to social services in Hispanic communities showed evidence of effectiveness among racial, ethnic and cultural minorities (Herbst et al. 2007).

Occupation

Not considered in included studies.

Gender/Sexuality

Gender and/or sexual orientation was addressed as a potential co-occurring disadvantage factor in four reviews. One looked at the effectiveness of gender- and culturally adapted interventions for Latino men, and found positive, albeit weak evidence of reduced drug use among the subpopulation compared to standard treatment (Valdez et al., 2018). Another looked at transgender and sexual minority youth and found two primary studies reporting positive results from community-based services with individualized treatment plans for sexual and gender minorities (Coulter et al., 2019). The third review looked specifically at effectiveness of interventions in reducing prenatal or postpartum drug use among women of childbearing age and found inconclusive evidence of effectiveness of online technology-based interventions from five relevant primary studies (Hai, Hammock, et al. 2019). Lastly, while not explicitly focused on gender/sexual minority subpopulations, the fourth review looked at homeless youth as stratified by gender and found that homeless girls were likely to derive greater benefit from drop-in centres and shelters compared to boys in terms of reduced drug use frequency (Wang et al. 2019).

Education

One meta-analysis specifically focused on emerging adults in a non-college setting (Davis, Smith, and Briley 2017). The authors explicitly stated that most illicit drug interventions for emerging adults were evaluated within a college environment and individuals without university education may not only be at higher risk of harmful drug use but may also react differently to existing interventions than college students and graduates. The review authors found that targeted personalized feedback interventions, commonly associated with high effectiveness among emerging adults in college settings, had inconclusive results among their less educated peers with SUD. Other targeted interventions targeted for individuals with SUD, such as motivational

interviewing in community setting showed effectiveness among non-college educated emerging adults.

Socioeconomic Status

We identified one meta-analysis that explicitly examined community engagement drug intervention effectiveness for individuals of low socioeconomic status (O'Mara-Eves et al. 2015). This was part of a large-scale statistical synthesis of community-level public health interventions for a broad set of health behavioral outcomes among disadvantaged communities. The review reported that community engagement interventions targeted at people of low socioeconomic status were particularly effective at reducing existing illicit drug use.

Social Capital

Not measured in included studies.

Plus 1: Age

Twenty-two reviews examined age as a potential disadvantage factor for the risk of illicit drug use and differential effectiveness of interventions. Of those, 6 looked at age without considering additional co-occurring PROGRESS-Plus domains and examined effectiveness specifically for children, adolescents, and young adults under 25 years old. The remaining 16 studies examined intervention with respect to at least one additional disadvantage factor, namely ethnicity, vulnerable place of residence (i.e., homelessness, rural setting), existing SUD and mental health problems, low educational attainment, sexual minority status and time-dependent life events (i.e., leaving out-of-home care or failing school).

Among reported intervention types, universal school-based educational interventions for prevention of illicit drug use were the most represented (Hale, Fitzgerald-Yau, and Viner 2014, Bonar et al. 2020, Hendricks Brown et al. 2007, Stockings et al. 2016). The effectiveness of these interventions appears to be inconclusive across studies, with multiple reviews coming to divergent conclusions regarding the effectiveness of these interventions. However, one large-scale review reported positive effects on drug use among children in rural setting (Hendricks Brown et al. 2007). Generally, reviews reported that involving parents in the school community-based interventions through family-school partnerships appears to have a positive effect on drug use frequency among

children and adolescents (Bonar et al. 2020, Hale et al. 2014). Other universal interventions included mass media prevention campaigns (O'Mara-Eves et al., 2015, Mewton et al., 2018) and public policy measures, such as police and law restriction (Stockings et al. 2016). These types of interventions showed either mixed or inconclusive findings. Targeted interventions reported in included reviews, were generally brief, and included motivational interviewing for youth with SUD (Li et al. 2016), culturally adapted interventions for ethnic minority youth (Snijder et al., 2020), online interventions for women of childbearing age (Hai, Hammock, et al. 2019), or skill building and reintegration interventions for homeless or street-connected youth (Coren et al., 2016). Most of these targeted interventions showed inconclusive or null results, apart from culturally adapted interventions for Indigenous youth which are associated with decreased drug use among the subpopulations.

Plus 2: Disabilities and comorbidities

Disabilities and co-morbidities as a disadvantage domain category focused exclusively on the intersection of mental health and substance dependence in intervention evaluations. Overall, 7 reviews addressed mental health disorders, such as depression or suicidal thoughts for a range of subpopulations, including adolescents (Salvo et al., 2012), ethnic minorities (Guerrero et al., 2013, Leske et al., 2016), or victims of violence with post-traumatic stress disorders (Sabri et al., 2019).

One review reported that culturally adapted interventions for Latino males with dual disorders showed promising results of effectiveness in drug use reduction, compared to standard treatment (Guerrero et al., 2013). Another review reported inconclusive results of culturally adapted interventions for Indigenous adults with mental health problems (Leske et al., 2016). Comprehensive, multi-component interventions for substance-abusing victims of violence appeared effective at reducing severity of drug use (Sabri et al., 2019). Universal secondary prevention interventions appeared effective, while skills-based primary prevention programs demonstrated mixed effectiveness for adolescents with mental health difficulties and SUD (Salvo et al., 2012).

Other important disabilities that could contribute to increased illicit drug use and/or differential treatment effectiveness, including physical impairments, such as blindness, partial paralysis, or co-

occurring serious illnesses such as cancers, cardiovascular illnesses, or diabetes, were not addressed in any reviews.

Plus 3: Substance use disorders (SUD)

Thirteen reviews addressed individuals with SUD, such as existing alcohol or drug dependencies, in their intervention evaluations. Five of these looked at SUD as the sole PROGRESS-Plus domain irrespective of other characteristics, and eight included additional co-occurring risk-factors, such as young age (Li et al., 2016, Carney & Myers, 2012), vulnerable place of residence (Miler et al., 2020, Paquette & Pollini, 2018), or time dependent life events, including existing criminal charges (Brown 2010).

Six reviews reported findings on the effectiveness of universal prevention interventions, such as safe injection sites or pharmacy-delivered needle-exchange programs, to reduce the risk of HIV transmission associated with injectable drug use and needle sharing. These programs appeared particularly effective for PWID in general and homeless individuals with existing SUDs in urban areas (Miler et al. 2020), but were not effective for PWID in rural areas due to a lack of geographical accessibility (Paquette & Pollini, 2018). Drug treatment courts generally appeared effective at reducing drug use among criminal offenders with SUDs (Brown, 2010, Wittouck et al., 2013).

Plus 4: Time-dependent life events (TDLF)

Time-dependent life events, such as recent release from prison, out-of-home facility, school failure or experience of domestic violence and substance use were addressed in nine reviews. All interventions reported in included reviews were targeted for the specific time-dependent life experience. Provision of drug treatment courts, social services and education in the periods leading up to and after release from prison appeared effective at reducing drug use frequency (Kouyoumdjian et al. 2015, Brown, 2010, Wittouck et al., 2013).

Similarly, behavioral couples therapy for co-abusing spouses and partners, as well as multi-component interventions for violence victims showed promising effectiveness in reducing drug use (Ruff et al. 2010, Sabri et al., 2019). Transition programs for youth leaving-out of home care did not appear effective at reducing drug use frequency (Heerde et al. 2018).

No reviews looked at the effectiveness of universal interventions for individuals who recently experienced a significant and sudden life change, which could affect their current ability to access and benefit from the resources universally available.

Discussion

Overview of findings

This paper provided an overview of published systematic reviews reporting effectiveness of illicit drug interventions for at least one PROGRESS-Plus subpopulation.

Over the last two decades, there has been a significant increase in the number of systematic reviews that evaluate effectiveness of illicit drug interventions with respect to different subpopulations at risk. However, we found that some subpopulations were excluded from most, or all intervention evaluation systematic reviews within the field of illicit drug use. These subpopulations include individuals with low occupational and educational attainment, socioeconomic status, and social capital. We also found that within the broad PROGRESS-Plus domains represented in systematic reviews, some specific subpopulations are missing in intervention evaluation. For example, while age was a well-represented PROGRESS-Plus domain, no reviews looked at old age as a potential source of disadvantage both in terms of increased risk of drug use, and potentially differential intervention effectiveness. Similarly, within the domain of Disabilities and Comorbidities, all reviews focused on mental health, and none addressed physical disabilities, such as blindness, deafness, or mobility impairments. Given the persistent evidence that drug use patterns differ markedly between persons with PROGRES-Plus disadvantage traits relative to those without, this seems like a serious missed opportunity and a research gap for future researchers.

Moreover, we found that not all intervention types received the same attention when it comes to subpopulation-specific evaluation. Most reviews presented findings for interventions targeted at specific PROGRESS-Plus subpopulations, such as case management interventions for homeless individuals, or culturally adapted interventions for ethnic minorities. Few reviews reported subpopulation-specific findings for large scale, universal interventions in the public health or policy domain, such as mass media campaigns or environmental prevention programs. Most reviews did not explicitly exclude universal interventions from their review focus, but there

appears to be a lack of primary studies that examine universal illicit drug intervention effectiveness through the lens of PROGRESS-Plus subpopulations. This is an important finding, for it uncovers gaps in our current understanding of who benefits from existing universal interventions. For example, we have no systematic and synthesized understanding of how effective universal illicit drug interventions are for, among others, individuals who have been victims of violence, recently released from prison, or living with significant physical impairments. Understanding how universal interventions affect subpopulations is imperative for addressing persisting health inequities.

Apart from uncovering important gaps in subpopulation representation in knowledge syntheses within the field, we outlined general trends in the types of interventions that appear to be effective for specific subpopulations, as defined by their membership in one or more PROGRESS-Plus domains. Overall, we found consistent evidence of effectiveness of targeted, culturally adapted and language specific interventions for racial, ethnic, and cultural minorities, who may not be able to benefit proportionately from standard universal interventions available. Similarly, we found evidence from multiple reviews pointing towards effectiveness of drug treatment courts for criminal offenders with SUDs, and syringe exchange programs and safe injection sites for PWID.

While these reductions in drug use were consistent across reviews, most effects were reported as small to moderate and short-term. Long term reduction in harmful illicit drug use was seldom reported and when reported, the intervention effects were often not persistent over time. Reviews that reported mixed or inconclusive effectiveness of interventions suggest that rather than reducing illicit drug use, the interventions analysed may have shifted consumption patterns from hard drugs to softer drugs and alcohol (Coren et al. 2016).

Table 4: Systematic reviews of interventions for individual PROGRESS-Plus factors

PROGRESS-Plus Domain	Setting	Population	Outcome of Interest	Policy Type	Intervention Details	Effect on Health	N° of relevant articles	Review
Place of Residence	OECD HIC	Inner-city or rural population	Drug Use Frequency	Universal	Public-health interventions such as community-setting interventions	0	18 (131)	(O'Mara-Eves et al. 2015)
		Homeless or vulnerably housed population	Drug use reduction	Targeted	Case Management Interventions (Intensive vs Standard)	+/-	22 (56)	(Ponka et al. 2020)
						*	4 (21)	(de Vet et al. 2013)
	USA, CAN			Targeted	Emergency department interventions, including case management interventions for drug use reduction (intensive vs standard case management)	*	4 (13)	(Formosa et al. 2021)
Race/ Ethnicity/ Culture	USA	Indigenous population	Drug use prevention	Targeted	Culturally grounded, deep-structure prevention interventions	+	5 (14)	(McLean et al. 2020)
		Non-white black and Hispanic population	Intravenous drug use	Targeted	Multi-level targeted education and training interventions in schools through external consultant delivery	+/*	3 (26)	(Gorin et al. 2012)
			Drug use frequency	Targeted	Culturally appropriate and language-adapted motivational enhancements and integrated treatments for substance abuse disorders at community level	*	5(100)	(Guerrero et al. 2013)
	OECD HIC			Universal	Large-scale public-health interventions such as community-setting interventions	+	18 (131)	(O'Mara-Eves et al. 2015)
	USA	Hispanic, Latino population	Drug use and HIV risk	Universal	HIV behavioral prevention interventions, personal skills	+	7 (20)	(Herbst et al. 2007)
				Targeted	Referrals to social services, job placements in Hispanic communities, adapted to Hispanic culture and Spanish	+		
Socio-economic Position	OECD HIC	Low socio-economic status population	Drug Use	Targeted	Public-health interventions such as community-setting interventions, tailored mass media programs	+	36 (131)	(O'Mara-Eves et al. 2015)
				Universal	Universal mass media or health care setting interventions	*		
Plus 1: Age	OECD HIC	Youth population	Drug use frequency	Universal	School-based interventions and family-school partnerships, web-based interventions	+/*	31 (55)	(Hale et al. 2014)
				Targeted	Targeted school and family-based interventions for youth	+		
	OECD HIC		Drug use frequency	Universal	Media campaigns for prevention of illicit drug use, anti-Illicit drug public service announcements	*	20 (52)	(Mewton et al. 2018)
	USA		Drug use frequency	Universal	School community-based interventions for youth and their parents	+	2 (76)	(Bonar et al. 2020)
	OECD HIC		Cannabis use	Targeted	Brief, computerized interventions for early stages of substance use delivered for a short duration of time, such as assessment, feedback, and decision-making modules	0	7 (60)	(Smedslund et al. 2017)

PROGRESS-Plus Domain	Setting	Population	Outcome of Interest	Policy Type	Intervention Details	Effect on Health	N° of relevant articles	Review
Plus 1: Age	OECD HIC	Youth population	Drug use and prevention	Targeted	College education interventions, screening and brief interventions, motivational enhancement, peer self-help, family-based interventions, juvenile drug courts	*	291 (414)	(Stockings et al. 2016)
				Universal	Sales restriction, police and law enforcement, scheduling under international conventions, mass-media, or education interventions	+/-		
Plus 2: Disabilities and co-morbidities		Individuals with mental health and drug use disorder	Drug use reduction	Targeted	Digital computer and mobile phone technology-assisted interventions for co-morbid depression and substance use	+	3 (6)	(Holmes et al 2019)
						+	33 (33)	(Dugdale et al. 2019)
	UK, USA		Drug use reduction		Integrated mental health and substance abuse services in community primary care setting	+	8 (12)	(Atun et al. 2011)
Plus 3: SUD	OECD HIC	Heavy drug users and PWID	Drug overdose	Universal	Provision of supervised injection services for safe drug use	+	75 (75)	(Potier et al. 2014)
	USA		Injectable drug use risk - HIV		Syringe and needle exchange programs delivered through public health interventions in a community pharmacy setting	+	28 (15 reviews)	(Thomson et al. 2019)
	OECD HIC		Injectable drug use risk - HIV	Universal	Secondary material + environmental prevention programs	*	N/A	(Fischer et al. 2015)
				Targeted	Psychosocial treatment interventions	+	N/A	
					Targeted, community-based prevention interventions		N/A	
	USA	Drug users in recovery	Substance use	Targeted	Peer-delivered recovery support services for drug addictions	+	9 (9)	(Bassuk et al. 2016)
		PWID	Injectable drug use risk - HIV	Universal	Pharmacy-delivered non-prescription syringe distribution services	+	29 (47)	(Janulis 2012)
Plus 4: TDLE	All	Frequent ED users	Drug use frequency	Targeted	Clinical Case-management interventions for frequent ED users	+/*	3 (11)	(Althaus et al. 2011)
		People in or released from prisoned	Drug use frequency		Motivational interviewing during imprisonment, educational and skills building programs during imprisonment, services after release	+	24 (95)	(Kouyoumdjian et al. 2015)
	USA	Substance-abusing couples	Drug abuse and family violence		Behavioral Couples Therapy for substance abuse treatment	+	23 (23)	(Ruff et al. 2010)

Table 5: Systematic reviews of intervention effectiveness for multiple co-occurring PROGRESS-Plus factors

PROGRESS-Plus Domain	Setting	Population	Outcome of Interest	Policy Type	Intervention Details	Effect on Health	N° of relevant articles	Review
Place of Residence + Plus 1: Age	USA	Children in rural setting	Drug Use	Universal	School-based drug prevention programs	+	182 (182)	(Hendricks Brown et al. 2007)
	USA, KOR	Street-connected children	Reduced drug use	Targeted	Interventions for promoting reintegration and harmful behavior reduction in street-connected youth	+/-	11 (13)	(Coren et al. 2016)
Place of residence + Plus: 3: SUD	OECD HIC	Substance- abusing homeless individuals	Drug use frequency + reduction	Targeted	Peer-support provision to and from individuals with lived experience	+	34 (62)	(Miler et al. 2020)
				Universal	Safe/supervised safe injection sites	+		
	USA	PWID among non-urban dwellers	HIV risk attributable to injective drug use	Targeted	Partner notification program for individuals who tested positive for HIV	+	26 (34)	(Paquette and Pollini 2018)
				Universal	Clean syringe access in non-urban pharmacies and other secondary sources, HIV testing and syringe exchange program HIV risk reduction interventions	-		
		Homeless people with SUD	Drug use reduction	Targeted	Case management interventions, post-detoxification stabilization programs and therapeutic community	+/*	41 (73)	(Hwang et al. 2005)
				Universal	Drop-in centres, community facilities	*		
Plus 1: Age + Education	OECD HIC	Emerging adults in non-college settings	Drug use reduction or prevention	Targeted	Prevention and treatment interventions, such as motivational interviewing, personalized feedback, and e-interventions	+	50 (50)	(Davis et al. 2017)
Plus 1: Age + Plus 3: SUD		Adolescents with SUD	Change in drug use	Targeted	Early, brief interventions with a drug use screening and intervention component	+	9 (9)	(Carney and Myers 2012)
			Drug use frequency and attitudes	Targeted	Motivational interviewing interventions in primary care setting, implemented through a person-centered, conversational style encouragement to reduce drug use	0	9 (10)	(Li et al. 2016)
Plus 1: Age + Plus		Adolescents with mental health and drug use disorders	Substance use prevention	Targeted	Skills-based primary prevention programs	+/-	8 (8)	(Salvo et al. 2012)
				Universal	Secondary prevention interventions for substance use disorders in youth with mental disorders	+		
Gender/ Sexuality + Race/ Ethnicity/ Culture	USA	Latino men	Drug use outcomes	Targeted	Gender adapted or culturally adapted interventions for SUD treatment compared with standard treatment	+/0	7 (12)	(Valdez et al. 2018)
Gender/Sexuality + Plus 1: Age		Sexual- + gender minority youth	Drug use reduction	Targeted	Community-based services with individualized treatment plans	+	2 (12)	(Coulter et al. 2019)

PROGRESS-Plus Domain	Setting	Population	Outcome of Interest	Policy Type	Intervention Details	Effect on Health	N° of relevant articles	Review
Gender/ Sexuality + Age + Race/Ethnicity/ Culture	USA, NLD	Women of childbearing age (18-45), by ethnicity	Prenatal and/ or postpartum drug use	Targeted	Dynamic technology-based interventions, delivered online or through text messages and apps, for preventing/decreasing drug use among women on childbearing age	*	5 (15)	(Hai, Hammock, et al. 2019)
Race/ Ethnicity/ Culture + Plus 1: Age	USA	Indigenous youth population	Drug use prevention, and refusal skills	Targeted	Culturally specific interventions for indigenous youth	*	4 (34)	(Edwards et al. 2010)
					Culturally informed substance abuse interventions, such as those that avoid the separation of mind and body	+	14 (14)	(Liddell and Burnette 2017)
				Universal	Multi-cultural interventions for drug use and misuse	-		
	OECD HIC	Indigenous adolescents	Drug use prevention and use frequency	Targeted	Culture-based, culturally adapted programs for indigenous youth, such as language specific circle conversations, prayers and dancing in school, community and/or family setting	+	18 (26)	(Snijder et al. 2020)
		Non-white ethnicity youth population	Drug use prevention	Universal	Community-based and school-based programs involving peer-support training.	+	20 (52)	(Mewton et al. 2018)
	USA			Targeted	Culturally grounded prevention interventions for ethnic minority youth	+	12 (33)	(Lauricella et al. 2016)
		African American youth	30-day drug use	Targeted	Culturally grounded hip-hop based interventions for African American youth	*	1 (23)	(Robinson et al. 2018)
Race/Ethnicity/ Culture + Gender + Plus 1: Age	OECD HIC	Young people of different gender and ethnic profiles	Drug use prevention	Targeted	Behavioral counselling interventions, (i.e., perinatal home visits to pregnant Native American youth, or girls in foster care)	+/-	29 (29)	(O'Connor et al. 2020)
				Universal	Universal drug prevention interventions (i.e., computer-based interventions	+/-		
Place of residence + Plus 1: Age + Race/ Ethnicity/ Culture or Gender		Homeless youth of different gender and ethnic profiles	Drug use frequency	Targeted	Skill building programs, individual and family level therapies	+/*	15 (22)	(Wang et al. 2019)
				Universal	Structural interventions (such as housing support, drop-in centres, and shelters)	+/*		
Race/ Ethnicity/ Culture + Plus 2: Disabilities and co-morbidities	USA	Latino population with mental health and drug disorders	Drug use frequency	Targeted	Culturally appropriate and language-adapted motivational enhancements and integrated treatments for dual disorders at community level	+	5 (100)	(Guerrero et al. 2013)
	OECD HIC	Indigenous adults with mental health and drug abuse disorders	Drug use frequency	Targeted	Culture-based and culturally adapted interventions for indigenous populations	*	7 (16)	(Leske et al. 2016)
				Universal	Interventions that have not been systematically modified for indigenous population context	*		

PROGRESS-Plus Domain	Setting	Population	Outcome of Interest	Policy Type	Intervention Details	Effect on Health	N° of relevant articles	Review
Plus 1: Age + Plus 4: TDLE	USA	Youth leaving out-of-home care	Drug use frequency	Targeted	Transitional programs for youth leaving out-of-home care	0/*	4 (19)	(Heerde et al. 2018)
		Youth failing school or delinquent	Drug use reduction	Targeted	Mentoring interventions, where the mentee interacts with the professionally trained mentor over extended time	*	6 (46)	(Tolan et al. 2013)
Plus 3: SUD + Plus 4: TDLE		Incarcerated individuals with drug use disorders	Opioid use and overdose	Targeted	Interventions for prevention of opioid overdose fatality, such as screening brief interventions, referral to treatment and civil commitment	0	13 (13)	(Sugarman et al. 2020)
			Drug use reduction	Targeted	Drug-treatment courts that target underlying drug addiction of criminal offenders through treatment service provision in conjunction with judicial supervision	+	5 (44)	(Brown 2010)
	USA, AUS	Substance-using criminal offenders	Drug use	Targeted	Drug treatment courts and family treatment or dependency drug courts	+/*	10 (16)	(Wittouck et al. 2013)
Plus 2: Disabilities and co- morbidities + Plus 3: SUD + Plus 4: TDLE	All	Substance- abusing victims of violence with mental health disorders	Drug misuse, abstinence, use severity	Targeted	Comprehensive, multi-component, peer-delivered and brief interventions with a combination of components that addressed two or more syndemic outcomes (i.e., violence, mental health, substance misuse, HIV risk) for victimized substance-using individuals	+	10 (17)	(Sabri, Greene, and Lucas 2019)

+ Beneficial effect
- Negative effect
+/- Mixed effect
* Inconclusive
0 Evidence of no effect

Strengths and limitations

In undertaking this review, we faced challenges due to the heterogeneity of the included populations and interventions. For this reason, while we completed all necessary components of an umbrella review methodology, including a standardized data extraction form and a full quality appraisal using AMSTAR 2, our findings cannot offer a specific and unified set of effective intervention recommendation for illicit drug outcomes (Aromataris et al. 2020). This lack of concrete policy recommendations, commonly associated with focused umbrella reviews, was an anticipated limitation given our review design, since heterogeneity across all PICO elements has been identified as a major limitation of systematic reviews in social science (Davis et al. 2014). Instead, we produced an overview of subpopulation representation in systematic reviews within the field of illicit drug intervention evaluation, and general trends in the types of intervention design that appears to be effective for specific PROGRESS-Plus disadvantaged subgroups.

Another important challenge associated with heterogeneity of study designs included in this umbrella review, is that not all systematic reviews have a uniform risk of bias. Some reviews, for example, include primary study at higher risk of bias, such as cross-sectional studies or uncontrolled studies. The inclusion of such studies may have biased the intervention effectiveness results presented in the systematic reviews and subsequently in our umbrella review. However, the primary aim to provide an overview of existing reviews with subpopulation program evaluations remains unaffected.

While using PROGRESS-Plus proved to be an efficient way to cover a broad range of disadvantage characteristics and may represent a useful tool to standardize subpopulation intervention evaluation in future research syntheses, there are notable limitations associated with using the classificatory framework in its current form. Even though it offers researchers the flexibility to identify and add subject-specific disadvantage domains through the ‘plus’ component, some of the original PROGRESS domains may not work well for the purposes of subpopulation representation mapping analysis, because they do not offer mutually exclusive and separate domains. For example, disadvantaged occupational status, low educational attainment level and socioeconomic status are all separate domains within the framework, yet the two former domains could also be considered as dimensions and proxy measurements of the latter. This is not particularly troubling

when using PROGRESS-Plus as a reference framework for potential sources of disadvantage, but it may be an important issue when using it as a classificatory framework for assessing subpopulation representation in intervention evaluations. This is because it may lead us to conclude that some disadvantage dimensions, such as socioeconomic status, may be underrepresented, while in fact the dimension representation has been dispersed across its common proxy measurements. In the context of our findings, however, this particular SES misclassification issue does not apply, for we can safely conclude that both SES and its common proxy measurements of occupational status and educational attainment are underrepresented in illicit drug intervention evaluation syntheses.

A further potential challenge to this review was publication bias. Prior to the review, and to inform the development of the 'plus' factors as part of the PROGRESS-Plus framework, we conducted an extensive literature review of existing evidence about disadvantage dimensions associated with excess risk of illicit drug use and associated comorbidities. However, there is a possibility that some potentially relevant subpopulations outside the PROGRESS-Plus framework have been left out of illicit drug research due to consistently insignificant findings and could not be identified during our initial literature review. Similarly, authors of primary studies of illicit drug intervention effectiveness may have failed to pick up statistically significant differences in effectiveness across subpopulations and have consequently chosen to exclude subpopulation analysis from the published findings. As a result, there may not be enough primary studies available to warrant the conduct of subpopulation-level intervention effectiveness systematic reviews. In parallel, any subgroup analysis, whether in primary studies or knowledge syntheses, should be based on plausible theory. It may be inappropriate or implausible for every study to estimate different effects within every PROGRESS-Plus domain. Sub-group analyses should also be planned a priori, and typically require large sample sizes. This may be challenging especially for small subgroups, such as sexual minorities. As a result, there are important cost implications associated with ensuring that sample sizes are sufficient to conduct relevant subpopulation analyses in primary studies, which may represent a pragmatic limit on the possibility of subpopulation analyses in systematic reviews and meta-analyses.

It is also important to note that most of the reviews included in this paper have not used a comparative methodology. Consequently, we cannot evaluate whether the policies deemed as effective for a particular subgroup are more, or less effective than other existing alternatives or whether the intervention effectiveness differs for the subpopulation at risk compared to a general population comparator. We cannot, therefore, make conclusions about the types of interventions most effective for specific subpopulations, but rather report general trends in effectiveness of interventions currently evaluated in existing systematic reviews. This inability to draw specific conclusions and tightly control for a comparative study design of primary studies is a result of the necessary abstraction and loss of detail that resulted from our scoping focus on heterogenous previous reviews, rather than primary studies. However, we found that such level of breadth and abstraction was necessary for our primary purpose of mapping the representation of subpopulations in illicit drug intervention evaluation systematic reviews. Ideally, we would have conducted a de novo review of all primary studies using a consistent methodology, but such a commitment was not possible given our time constraints.

Despite these limitations, however, the finding that some PROGRESS-Plus domains are not at all represented in existing systematic reviews of illicit drug interventions is both relevant and important to highlight the need to produce new impactful evidence syntheses of subpopulation-specific illicit drug program evaluations.

Implications for future research

Our findings shed light on existing gaps in the evaluation of illicit drug interventions for certain disadvantaged subpopulations. Future researchers in the field should examine the effectiveness of illicit drug interventions for individuals with vulnerable occupational status, social capital, lower educational attainment, and socioeconomic status in general. Moreover, most interventions evaluated in the included reviews were targeted, as opposed to universal. More research is needed to shed light on the effectiveness of universal policies on illicit drug outcomes among subpopulations at-risk, as contrasted with a general population comparator.

Moreover, researchers in other related policy evaluation fields should consider the potential existence of implicit biases and inequities from the failure to evaluate intervention effectiveness

for all relevant stakeholders. We hope that the methodological approach used in this paper can be adapted to other policy evaluation areas and can present future equity-concerned researchers with an efficient and standardized way of evaluating whether their respective subfields assess existing interventions with respect to various relevant subpopulations at risk. Using PROGRESS-Plus has proved to be an effective way to quickly classify and map the extent of current subpopulation inclusivity in systematic reviews on illicit drug intervention effectiveness. The same approach can be adopted for other fields to potentially uncover broader evidence for persistent exclusion from impactful research across different health outcomes. While this review does not pertain directly to implementing evidence-based illicit drug interventions, it provides novel and relevant findings pointing to the need to evaluate interventions through the lens of an equity framework.

Conclusions

In conclusion, we found that systematic reviews of illicit drug intervention effectiveness were limited with respect to their focus on the following subpopulation characteristics: disadvantaged occupational status, low educational attainment, religion, socioeconomic status, and social capital. Among the most notable interventions evaluated in included reviews, community level, school- and family-based illicit drug intervention strategies appeared to be effective for youth populations. For racial, ethnic, and cultural minorities, we found a general trend in effectiveness of culturally relevant and language-adapted targeted interventions. Mass media and digital interventions have generally showed mixed effectiveness.

In their efforts to curb societal health inequities, academic researchers wishing to conduct future systematic reviews in the field should consider including underrepresented subpopulations in upcoming intervention evaluations.

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Appendix A

PROGRESS-Plus Factors and their individual relevance to illicit drug use

Place of residence

Residence in a disadvantaged area with potentially limited access to care (i.e., rural areas), high crime rates and drug availability (i.e., inner city urban areas), or homelessness may all negatively affect individuals' ability to resist drugs and seek help for misuse (Rhew et al. 2011, Mack 2017, Tyler et al. 2014).

Race/ethnicity/culture

Ethnic, racial, and cultural minorities or individuals who commonly speak a non-dominant language in their region of residence (i.e., individuals with African American, Hispanic, or Indigenous origins), may face discrimination and additional challenges related to illicit drug use and/or access to health and social services compared to their Caucasian counterparts (Newcomb et al. 2014, Delahunty and Putt 2006).

Occupation

Under-employment, unstable employment, work in unsafe conditions and joblessness, as well as a lack of employee benefits, insurance plans and other undesirable working conditions may negatively affect individuals' ability to resist drugs, seek help for substance use and recover (Henkel 2011, MacDonald and Pudney 2000).

Gender/sexual orientation

Gender self-identification and non-heterosexual orientation may affect individuals' perception of support available, exposure to violence, discrimination, drugs, and stigma associated with illicit drug use and help seeking (Newcomb et al. 2014).

Religion

Religiosity is commonly described as a protective factor against substance use in existing literature, affecting individual's perception of, and resilience to initiating illicit drug use (Dudley, Mutch, and Cruise 1987, Engs and Mullen 1999). Due to the body of evidence suggesting this predominantly protective nature of religiosity when it comes to illicit drug use outcomes, we decided to omit religion as a disadvantage factor for drug use from our analyses.

Education

Individuals with low educational achievement level (i.e., high school degree or lower) may be less likely to benefit from existing interventions than their more educated peers. Low educational achievement is also a multifaceted disadvantage factor associated Low educational achievement is also a multifaceted disadvantage factor associated with a high probability of co-occurring occupational disadvantage, low socio-economic status, and residence in a disadvantaged area; all strongly associated with an increased risk of drug use and inability to access necessary help (Chatterji 2006).

Socioeconomic status

Low socioeconomic status, commonly co-occurring with low education level, residence in a disadvantaged area, and occupational instability can affect the ability of individuals to access and/or afford health promoting resources and render them more vulnerable to harmful drug use than their wealthier counterparts (Gerra et al. 2020).

Social capital

Low social capital (i.e., insufficient community network, family relationships and loneliness) may affect the availability of social support and resilience to drugs. Insufficient social network may render individuals more vulnerable to peer pressure and may significantly affect successful recovery after drug use initiation (Åslund and Nilsson 2013).

+ Plus 1: Age

Teenagers and young adults may be significantly more vulnerable to drug use initiation and peer pressure than other age groups, more likely to find access to and experiment with illicit drugs (Lynskey et al. 1999). Similarly, research evidence suggests that children and young persons may have less impulsivity control than older individuals, due to incomplete brain development (de Wit 2009).

+ Plus 2: Disabilities and Comorbidities

Disabilities, such as mental health disorders, chronic pain, diabetes, learning difficulties and physical handicaps among other things may significantly affect quality and self-perceived value of life. These comorbidities may contribute to increased risk of illicit drug use as a coping

mechanism, while at the same time, drug use may lead to increased risk of developing further comorbidities, such as depression, chronic pain, or disabilities. They may also render individuals less likely to be able to access and benefit from available help (i.e., non-braille mass media interventions may be unsuitable for blind individuals) (Moore and Li 1998, Tyler et al. 2014).

+ Plus 3: Substance abuse disorders

Individuals with existing substance abuse disorders, such as alcohol, cigarette or soft-drug addictions may be more susceptible to initiate heavy drugs and develop addictions. They may also suffer from additional comorbidities associated with their existing substance use addition, such as depression (Carpenter et al. 2017).

+ Plus 4: Time-dependent life events

Other at-risk subgroups include individuals during important life transitions, such as released and incarcerated criminal offenders, who may have history of drug abuse or violence and face societal stigma, discrimination, and inability to find suitable employment. They may likewise not possess the same ability to access resources than their counterparts without a criminal record. Additional groups facing disproportionate challenges are, for example, co-abusing partners and individuals living with or next to drug abusing relatives and roommates. These individuals have increased access to drugs and risk of peer pressure (Cavacuiti 2004, Mumola and Karberg 2006).

Appendix B

Search Terms

Database: Ovid MEDLINE(R) ALL <1946 to March 31, 2021>
Search Strategy:
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1 inequal$.mp. or exp Healthcare Disparities/ or exp Health Status Disparities/ or exp Socioeconomic Factors/ or health inequality.mp. or health inequity.mp. (504987)
2 Progress-Plus.mp. or exp PROGRESS PLUS/ (39)
3 (ethnic$ or indigenous or non-white or Hispanic or black or African-American or asian).mp. (511308)
4 (socioeconomic status or employment status or unemploy$ or social capital or occupation or religion).mp. (77297)
5 (place of residence or rural or urban or neighbourhood or high risk environment or homeless$ or vulnerably housed or displaced or migrant or immigrant).mp. (400140)
6 (sexual orientation or LGBTQ+ or LGBT or gay or lesbian or bisexual or transgender or queer or gender or sex or male or female).mp. (12215981)
7 (at-risk age groups or youth or teenage$ or elderly or old or pensioners).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1421512)
8 (disability or disabled or handicapped).mp. (292698)
9 (vulnerable group$ or subpopulation$ or at-risk population or heavy drug users or addict$ or comcorbid$ or mental health or depression or survivor or suicide).mp. (806221)
10 (high-income or high income or high income OECD or United States or Canada or EU).mp. (1236454)
11 (systematic review or systematic overview or scoping review or review of evidence or umbrella review or meta-analysis or review of reviews or meta analysis).mp. (343589)
12 (public policy or policy or intervention$ or health promotion$ or program or programme or health education or campaign or media or counsel$ or advice or targeted or universal or targeted universal$).mp. (2969344)
13 illicit drug.mp. or exp Illicit Drugs/ or cannabis.mp. or exp Cannabis/ or drug abuse.mp. or exp Substance-Related Disorders/ or drug outcomes.mp. (312605)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (13500054)
15 10 and 11 and 12 and 13 and 14 (147)

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Database: Embase Classic + Embase <1947 to 2021 March 31>
Search Strategy:
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1 exp "systematic review"/ or exp meta-analysis/ or umbrella review.mp. or review of reviews.mp. or scoping review.mp. or meta analysis.mp. or review of evidence.mp. (493434)
2 (public policy or policy or intervention$ or health education or campaign or targeted intervention$ or universal intervention$ or targeted universal$).mp. (2126372)

3 illicit drug.mp. or exp Illicit Drugs/ or cannabis.mp. or exp Cannabis/ or drug abuse.mp. or drug outcomes.mp. or opioid.mp. (247902)
4 (high-income or high income or high income OECD or United States or Canada or EU or developed).mp. (4533051)
5 (vulnerable group$ or subpopulation$ or at-risk population or heavy drug users or addict$ or comcorbid$ or mental health or depression or survivor or suicide).mp. (1443244)
6 (disability or disabled or handicapped).mp. (390230)
7 (at-risk age groups or youth or teenage$ or elderly or old or pensioners).mp. (2316508)
8 (sexual orientation or LGBTQ+ or LGBT or gay or lesbian or bisexual or transgender or queer or gender or sex or male or female or religion$ or social capital).mp. (14120489)
9 (place of residence or rural or urban or neighbourhood or high risk environment or homeless$ or vulnerably housed or displaced or migrant or immigrant).mp. (501586)
10 (socioeconomic status or employment or unemploy$ or occupation or social capital).mp. (107939)
11 (ethnic$ or indigenous or non-white or Hispanic or black or African-American).mp. (761546)
12 (Progress-Plus or PROGRESS PLUS).mp. (48)
13 (inequal$ or Health$ Disparit$ or Socioeconomic Factors or health inequalit$ or health inequit$).mp. (86710)
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (15976849)
15 1 and 2 and 3 and 4 and 14 (249)

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EPISTEMONIKOS:
(abstract:(
systematic review OR review OR umbrella review or meta analysis or meta-analysis)
AND (policy OR intervention OR campaign OR education OR prevention OR promotion OR policies)
AND (substance abuse OR illicit drug OR drug OR opioid OR drug use)
AND (inequality OR disparity OR health inequality OR socioeconomic OR ethnic OR indigenous OR sexual OR minority OR minorities OR subpopulation OR homeless OR displaced OR at-risk OR vulnerable OR Hispanic OR African-American OR PROGRESS-Plus OR religion OR place of residence OR social capital)
AND (high-income OR OECD OR OECD high-income OR United States OR Canada OR Australia OR United Kingdom OR EU OR European countries))

****

GOOGLE SCHOLAR
(“systematic review” OR “review” OR “umbrella review” OR “meta-analysis” OR “meta analysis”)
AND (“policy” OR “intervention” OR “campaign” OR “prevention” OR “promotion” OR “policies”)
AND (“substance” OR “illicit drug” OR “drug” OR “opioid” OR “drug use” OR “injective drug use”)
AND (“inequality” OR “disparity” OR “health inequality” OR “socioeconomic” OR “ethnic” OR “indigenous” OR “sexual” OR “minority” OR “minorities” OR “subpopulation” OR “homeless” OR “displaced” OR “at-risk” OR “vulnerable” OR “Hispanic” OR “African-American” OR “PROGRESS-Plus” OR “religion” OR “Place of residence” OR “social capital”)
AND (“high-income” OR “OECD” OR “United States” OR “Canada” OR “Australia” OR “United Kingdom” OR “EU” OR “European countries”

Appendix C

Exclusion criteria for studies included in full text review

Study	Reason for exclusion
(Ferri et al. 2013)	Findings duplicated in a review of reviews (Mewton et al. 2018)
(Fletcher, Bonell, and Hargreaves 2008)	Findings duplicated in a review of reviews (Mewton et al. 2018)
(Werb et al. 2011)	Findings duplicated in a review of reviews (Mewton et al. 2018)
(Sack and Thomasius 2002)	Full text not in English
(Fernández, Nebot, and Jané 2002)	Full text not in English
(Akanbi et al. 2020)	Intervention evaluation for a PROGRESS-Plus domain missing
(Hai, Franklin, et al. 2019)	Intervention evaluation for a PROGRESS-Plus domain missing
(King et al. 2015)	Intervention evaluation for a PROGRESS-Plus domain missing
(Kouyoumdjian et al. 2015)	Intervention evaluation for a PROGRESS-Plus domain missing
(Leece et al. 2019)	Intervention evaluation for a PROGRESS-Plus domain missing
(Mauri, Townsend, and Haffajee 2020)	Intervention evaluation for a PROGRESS-Plus domain missing
(Werb et al. 2013)	Intervention evaluation for a PROGRESS-Plus domain missing
(Naar-King et al. 2009)	Wrong study design (not a systematic review)
(Rowan et al. 2015)	Wrong study design (not a systematic review)
(Russell et al. 2016)	Wrong intervention
(Sharma et al. 2020)	Full text not available
(Agabio et al. 2015)	Wrong outcome (illicit drugs not a separate outcome)
(Bagley et al. 2019)	Wrong outcome (effect on illicit drugs not quantified)
(Des Jarlais et al. 2013)	Wrong outcome (cannot link outcome to intervention)
(Lyles et al. 2007)	Wrong outcome (illicit drugs not a separate outcome)
(Mize et al. 2002)	Wrong outcome (illicit drugs not a separate outcome)
(Padmanathan et al. 2020)	Wrong outcome (cannot link outcome to intervention)
(Anderson et al. 2015)	Wrong outcome (insufficient evidence for illicit drug use)
(Bonell et al. 2013)	Wrong outcome (illicit drugs not a separate outcome)
(Carver et al. 2020)	Wrong outcome (effect on illicit drugs not quantified)
(Córdova et al. 2017)	Wrong outcome (insufficient evidence for illicit drug use)
(Getty et al. 2019)	Wrong outcome (medication adherence only)
(Stewart, Reilly, and Ward 2018)	Full text not available
(Haldane et al. 2017)	Wrong outcome (illicit drugs not a separate outcome)

Chapter 4: Manuscript 2

Preface

In this manuscript, we explore the changes in opioid and non-prescription drug use patterns and help-seeking behavior for substance misuse in Canada during the COVID-19 pandemic. We aim to determine how these changes relate to different PROGRESS-Plus characteristics in the Canadian population. This manuscript is in preparation for publication submission to the *Canadian Journal of Public Health*.

Changes in opioid use, non-prescription drug use and help-seeking behaviours in Canada during the COVID-19 pandemic

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MB was responsible for the concept, design, and main analysis of this study, as well as the written draft of the manuscript. AQV provided feedback on the concept and design of the study. All authors contributed critical revisions for important intellectual content as well as read and approved the final manuscript.

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Conflicts of interest
The authors declare that they have no conflicts of interest relevant to the content of this article.

Availability of data and material
The CPSS6 PUMF dataset is publicly available for download from Statistics Canada (https://www150.statcan.gc.ca/n1/pub/45-25-0012/452500122021001-eng.htm). Data analysis and coding from R Studio, version 1.2.1335 are available upon request.

Ethics approval
TCPS 2 Statement: Article 2.2: Research does not require Research Ethics Board review when it relies exclusively on information that is:

a) publicly available through a mechanism set out by legislation or regulation and that is protected by law; or
b) in the public domain and the individuals to whom the information refers have no reasonable expectation of privacy.

Consent to participate and publish
Not applicable

Abstract:

Objectives: The COVID-19 pandemic and the resulting uncertainty it brought has negatively impacted the lives and mental health of many Canadians and exacerbated barriers for people already suffering from anxiety and substance abuse problems. This paper assesses patterns of opioid use, non-prescription drug use and help-seeking behavior for substance misuse in Canada during the COVID-19 pandemic and explores how these changes relate to different sociodemographic characteristics in the Canadian population.

Methods: We used data from the Canadian Perspectives Survey Series 6 (CPSS6) dataset on substance use and stigma during the pandemic. Two analytic samples of complete cases were drawn from the dataset (N= 346 and 308), and a set of binomial logistic regression models was used to assess the associations between sociodemographic determinants of health and two primary outcomes: changes in drug use and help-seeking behavior for substance misuse. Odds ratios (ORs) and 95% confidence intervals were calculated and used to graphically portray the findings.

Results: We found a significant association between increase in both opioid and non-prescription drug (NPD) use and poor mental health outcomes during the COVID-19 pandemic. Compared to Canadians with 'excellent' mental health, those who self-rated their mental health as 'poor' were 8.1 and 5.7 times as likely to have increased their opioid and NPD use, respectively (Opioid OR: 8.11, 95% CI 2.99-22.75; NPD OR: 5.73, 95% CI 2.20-14.97), all else kept constant. When it came to help-seeking behavior, poor mental health was significantly associated with inability to find needed help. The odds of responding 'yes' as opposed to 'no' when asked if they were unable to find help for substance misuse were over 19 and 14 times higher for opioid and NPD users in poor mental health respectively, compared to those in 'excellent or good' mental health (Opioid OR: 19.48, 95% CI: 8.21-48.83; NPD OR: 14.81, 6.36-36.31), and we saw a clear gradient in increased inability to find help as mental health scores worsened. We also found that that the odds of being unable to find help were around twice as high for single Canadians compared to their partnered counterparts in the populations of both opioid and NPD users (OR: 2.9, 95% CI: 1.3-6.2). Results from supplemental analyses of the odds of response to opioid and NPD questions compared to a valid skip of the questions (i.e., a proxy for non-use of opioids and NPDs), revealed

that individuals in poor mental health and single, divorced, or widowed individuals were more likely to respond to both opioid and NPD use questions than those who rate their mental health as excellent or good and partnered individuals, respectively. Since the overall trends in consumption changes between NPD use and prescription or non-prescription opioid use, as well as the likelihood to respond to the survey questions were overwhelmingly similar, we can hypothesize that the relevance of the findings extends beyond mapping the changes in illicit drug use, to changes in legal use of pain management drugs during the COVID-19 pandemic in Canada as well.

Conclusions: Our findings raise awareness of comorbid mental health and drug use problems among Canadians during the COVID-19 pandemic and point to the need for accessible and targeted interventions for those unable to access much-needed help during the pandemic.

Keywords: Illicit Drugs, Opioids, Non-prescription Drugs, Unmet Needs, Social Determinants of Health, Canadian Population, COVID-19

Background:

The novel coronavirus disease 2019 (COVID-19), has been spreading internationally and disrupting lives worldwide since it was declared a pandemic by the WHO in March 2020. Since then, the pandemic has spurred an ebullient research enterprise, not only in understanding and mapping the clinical and epidemiological evolution of the disease, but also regarding how social determinants of health, including poverty, smoke exposure or homelessness, affect COVID-19 outcomes (Dhar Chowdhury and Oommen 2020), (Abrams and Szefler 2020). Surprisingly, however, research attention to the broader effects of the COVID-19 pandemic, including the effect of uncertainty, stress, and disruption to social services, on people's drug use patterns and help-seeking behavior has been limited. Most notably, Panchal and colleagues found that the pandemic exacerbated mental health and substance abuse disorders, not only through its direct amplifying effect on those behaviours, but also because it imposed new barriers on the availability of public resources and access to needed help (Panchal and Kamal 2021). Similarly, Horigian and colleagues document that COVID-19 particularly affected young people in the US, who now report significantly higher levels of comorbid loneliness, mental health problems and substance use (Horigian et al. 2021).

This paper has two objectives: (1) to estimate sociodemographic risk factors associated with increased consumption of opioids and non-prescription drugs during COVID-19, and (2) to document unmet needs for care and examine the extent to which drug-using Canadians seeking help for substance abuse or mental health problems experience difficulties in accessing public services during the pandemic.

It is especially pertinent to explore these two objectives in the context of Canada, given its ongoing opioid crisis, escalating overdose deaths and polarizing public attitudes towards the issue (Korzinski 2021). According to research from Angus Reid Institute, 70% of Canadians believe that opioid and non-prescription drug (NPD) addiction problems have worsened over the past year, while 48% fear the issue escalated in their own community (Korzinski 2021). Over the course of the COVID-19 pandemic, Canada witnessed an increase in the use of illicit injectable drugs and associated overdose deaths (Health Canada 2020). Moreover, individuals with existing substance use disorders, opioid addictions and in recovery are even more vulnerable during the pandemic

than before, because they may mistake symptoms of a SARS-COV-2 infection with addiction withdrawal symptoms and manage it by misusing opioids or other non-prescription drugs (Dunlop et al. 2020). However, personal characteristics and potential protective and risk factors associated with these changes in drug use in Canada are not currently understood. As its first objective, this paper aims to provide some evidence of the magnitude and direction of the changes with reference to many established social determinants of health.

The Government of Canada took action to support people at increased risk of overdose and morbidities associated with unsafe injection drug use by expanding access to safer drug supply and providing the right for provinces to establish temporary Urgent Public Health Need Sites for safe drug use within, for example, currently-closed supervised injection sites (Health Canada 2020). However, the success of these new initiatives to support Canadians suffering from either licit or illicit drug abuse amidst the COVID-19 pandemic has not been evaluated from the perspective of drug users. To this end, the current paper pursues a second objective, an evaluation of the extent to which Canadians needed help with substance misuse or mental health but could not access or receive it.

Together, the two objectives aim to provide a timely overview of changes in the use of opioids and non-prescription drug as well as help-seeking behavior for substance misuse during the COVID-19 pandemic in Canada with an understanding of how individual sociodemographic characteristics affect both outcomes of interest. The paper hopes to contribute to existing evidence of the widespread effects of the COVID-19 pandemic on the Canadian society beyond the traditional focus on curbing the spread of COVID-19 or managing associated caseload and hospitalizations.

Methods:

Data

We used data from a publicly available cross-sectional Public Use Microdata File (PUMF) dataset, '*Canadian Perspectives Survey Series 6: Substance Use and Stigma During the Pandemic*' (CPSS6) administered by Statistics Canada[6]. The CPSS6 frame for survey is Statistics Canada's

[6] This paper uses publicly available, encrypted, and anonymized dataset and, as such, was deemed exempt from a formal TCPS2 ethics approval review from Research Ethics Board, Government of Canada.

pilot probability panel, created by randomly selecting a subset of respondents from the Labour Force Survey (LFS). The LFS sample is drawn from an area frame and is based on a stratified design using probability sampling (Statistics Canada 2021a). Data for the CPSS6 dataset was collected using short online surveys from January 25, 2021, to January 31, 2021. Survey participation was voluntary and the survey was designed to produce data representative of the Canadian population aged 15 and over from all provinces (Statistics Canada 2021a). Overall, 7,242 CPSS panelists were eligible for the CPSS6 survey, of which 3,941 individuals responded, yielding a response rate of 54.4% (Statistics Canada 2021a). A mixed mode approach was used for nonresponse follow-up, inclusive of mailed and e-mail reminders, where available (Statistics Canada 2021a). All our analyses were weighted with LFS sample weights provided by Statistics Canada as part of the CPSS6 PUMF dataset.

Target population and analytic sample definition

Due to substantial missingness with respect to our main variables of interest (opioid[7] and NPD[8] use change during COVID-19[9]) and a lack of complete overlap between the opioid and NPD user population, our paper includes two separate analytic samples. The target population can be defined as Canadian adults and adolescents aged 15 and older, who reported past use of opioids (analytic sample 1) and NPD (analytic sample 2). Based on the question *'In the past 30 days, have you used any prescribed or non-prescribed drugs containing opioids?'* (analytic sample 1), and *'In the past 30 days, did you use any non-prescribed drugs?'* (analytic sample 2), individuals who responded *'Yes'* or *'No, not during the past 30 days'* were included in our analytic samples. Individuals who responded *'Never used any opioids'* (analytic sample 1) and *'Never used any non-prescribed drugs'* (analytic sample 2) were excluded from analysis, because their responses were considered as 'valid skip' of our main outcome variables of interest. We do not make sample exclusion based on age for two reasons. Firstly, illicit drug possession, cultivation and use, exclusive of cannabis, is considered a criminal offence for all age groups across Canada, as legislated by The Controlled

[7]CPSS6 defined opioids as products such as codeine, oxycodone, OxyContin, OxyNeo, hydromorphone, Dilaudid, morphine, fentanyl, methadone, Tylenol 1, 2, 3 or 4, 292s, Robaxacet-8, Percocet, Percodan, Demerol, AC&C, Mersyndol, Calmylin, and heroin for either medical or non-medical purposes (Statistics Canada 2021b).

[8]CPSS6 defined non-prescribed drugs as various substances, such as cocaine, crystal meth, amphetamines, ecstasy, hallucinogens, as well as the misuse of over-the-counter drugs with the purpose of getting high (Statistics Canada 2021b).

[9]Change in cannabis use was excluded from this analysis because it no longer constitutes an illegal substance in Canada since the enactment of the 'Cannabis Act' in 2018 (Health Canada 2018).

Drugs and Substances Act (Government of Canada 1996). Secondly, drugs including opioids can be prescribed irrespective of age.

Only complete cases with regards to all main variables were used in the regressions, missing values were uniformly recoded and excluded from the statistical analysis using listwise deletion, which significantly affected the sample size of both our two separate analytic samples. This is because only 9% and 7% of CPSS6 survey respondents reported previous opioid and NPD use, respectively, and were therefore deemed eligible for inclusion in our study (N= 346 and 308). According to the CPSS6 documentation, the remaining 3595 and 3633 of the CPSS6 survey participants previously responded that they have never used opioids (analytic sample 1) and non-prescribed drugs. (analytic sample 2), respectively. It is important to note that in the case of Analytic Sample 1, the outcome of interest, change in opioid use, covers the use of both prescribed and non-prescribed opioids, and therefore ostensibly includes both legal and illicit opioid consumption, but it is impossible to distinguish between the two. In the case of Analytic Sample 2, NPD use outcome is solely interested in misuse of non-prescribed substances, such as cocaine or hallucinogens.

Analytic sample 1: Opioid use during COVID-19: From the 3941 respondents of the CPSS6 survey, we excluded 3595 respondents (91.5% of the total sample) due to a valid skip of the main outcome variable of interest for analytic sample 1, *'Opioid use change'*, yielding an analytic sample of 346 respondents.

Analytic sample 2: NPD use during COVID-19: From the 3941 respondents of the CPSS6 survey, we excluded 3633 respondents (91.2% of the total sample), due to a valid skip of the main variable of interest for analytic sample 2, *'NPD use change'*, yielding an analytic sample of 308 respondents.

Informative valid skip and treatment of missing values: While in the main analysis, we considered individuals, who 'skipped' the questions related to drug use change or designated that these questions were 'not applicable to them', as 'missing', and excluded them from the analysis, we also hypothesize that this 'missingness' is informative.

Given this pattern of missingness, CPSS6 respondents excluded from our analytic samples 1 and 2 may either be those who never used opioids and NPDs, and hence questions about consumption changes during COVID-19 were not relevant to them (valid skip), or they may not wish to share their consumption patterns within the CPSS6 survey. Therefore, we could not consider missingness as random throughout our analytic samples. To exploit the possibility of valid skip to tell an additional story about potential protective factors associated with lower risk of opioid or NPD use, we chose to conduct two additional binary regression analyses using two new analytic samples, whereby we recoded both opioid use change (OPI_10) and NPD use change (NPD_10) variable into binary variables for valid responses (i.e. individuals who reported a history of past opioid or NPD use in a previous question) and valid skips (i.e., individuals who reported no drug use in a previous question and hence validly skipped OPI_10 or NPD_10). Therefore, in this additional analysis, we included individuals previously considered missing due to a valid skip of OPI_10 or NPD_10. This allowed us to construct two additional analytic samples of 3,932 and 3,934 individuals each, to test for characteristics associated with any level of opioid or NPD use, compared to a proxy for no use of opioids or NPDs.

Variables

Three dependent variables were included in the analysis, two of which were used towards Objective (1) to assess changes in opioid (analytic sample 1) and NPD use (analytic sample 2) during the COVID-19 pandemic among individuals who reported past opioid and NPD use. The survey response questions used to define these dependent variables were:

- Opioid use change (OPI_10): *On average, over the course of the COVID-19 pandemic, how has your use of opioids changed when comparing to before the pandemic?*
- NPD use change (NPD_10): *On average, over the course of the COVID-19 pandemic, how has your use of non-prescribed drugs changed when comparing to before the pandemic?*

One dependent variable was used towards Objective (2) to explore inability to find help for substance use, emotions, or mental health (included in both analytic samples as a proxy for unmet needs among opioid and NPD users, respectively). This dependent variable was explored

separately for both analytic samples, due to the possibility that patterns of unmet needs may differ by substance use type (i.e., among opioid and NPD users). The survey response question used to define this dependent variable was:

- HS_20: The survey response question was: *Since the beginning of the COVID-19 pandemic, was there ever a time when you felt you needed help for your emotions, mental health or use of alcohol or drugs, but you didn't receive it?*

See Appendix A for detailed descriptions of the CPSS6 questionnaire for the dependent variables. Independent variables consisted of eight sociodemographic respondent characteristics, namely age, sex, immigration status, marital status, highest education level, employment status. rural/urban indicator and mental health status. These covariates were chosen with reference to established research evidence on determinants of health behavior and drug use. Poor mental health is one of the most common comorbidities and a strong predictor of increased risk for both illicit drug initiation and drug use frequency (Burns et al. 2004, Burns and Teesson 2002, Stambaugh et al. 2017).

Similarly, research suggests that gender and sex also play a role in observed patterns of drug abuse and dependence, with men experiencing higher risk of hard drug initiation and rates of substance use overall, compared to women, while women appear to be more susceptible to dependence and addiction to both hard and soft drugs (Cotto et al. 2010, Moon et al. 1999). Recent research also revealed that immigration status, education level, marital status, age, employment status and place of residence may also influence health behaviors and illicit drug use (Peña et al. 2008, McDonald and Kennedy 2004, (Haider et al. 2009, DeSimone 2002, Cronk and Sarvela 1997, Scott et al. 2010, Musher-Eizenman, Holub, and Arnett 2003, Vang et al. 2017).

A list of descriptive statistics of all variables of interest for the full CPSS6 dataset as well as our two analytic samples is presented in Table 1 below.

Table 1: Descriptive Statistics for CPSS6, Analytic Sample 1 and Analytic Sample 2 (category-specific sample proportions in parentheses)

Independent variables		N° (Full CPSS6)	N° (Analytic Sample 1)	N° (Analytic Sample 2)
Opioid use change	Same/Decreased (reference)	318 (8)	318 (92)	/
	Increased	28 (1)	28 (8)	/
	Not applicable/ Valid skip	3595 (91)	0 (0)	/
NPD use change	Same/Decreased (reference)	269 (7)	/	269 (87)
	Increased	39 (1)	/	39 (13)
	Not Applicable/Valid Skip	3633 (93)	/	0 (0)
Unsuccessful help-seeking	No (reference)	3465 (88)	275 (80)	242 (79)
	Yes	450 (12)	68 (20)	66 (21)
Mental health	Excellent/good (reference)	3061 (77)	230 (66)	197 (65)
	Fair	678 (18)	73 (21)	71 (23)
	Poor	195 (5)	43 (13)	38 (12)
Immigration status	Born in Canada (reference)	3260 (83)	299 (86)	256 (83)
	Landed Immigrant	681 (17)	47 (14)	52 (17)
Education level	College or lower (reference)	2219 (56)	202 (58)	161 (52)
	University education	1722 (44)	138 (42)	147 (48)
Place of residence	Rural (reference)	825 (21)	60 (17)	60 (19)
	Urban	3116 (79)	285 (83)	248 (81)
Employment status	Employed (reference)	2295 (60)	180 (52)	184 (62)
	Unemployed	1545 (40)	153 (48)	113 (38)
Sex of respondent	Male (reference)	1808 (46)	142 (41)	146 (48)
	Female	2133 (54)	204 (59)	162 (52)
Marital status	Married/Common-Law (reference)	2477 (63)	194 (56)	169 (51)
	Single / Widowed/ / Divorced	1464 (37)	152 (44)	145 (49)
Age	15-34 (reference)	638 (16)	53 (15)	69 (22)
	35-64	2200 (56)	196 (57)	167 (55)
	65+	1103 (28)	97 (28)	72 (23)
Observations:		3,941	346	308

Analytic sample 1: Opioid use change during COVID-19: The distribution of key analytic sample characteristics revealed the following information about our independent variables: 86%

of respondents were born in Canada, 42% hold bachelor's degree or higher, 83% are urban dwellers, 48% are unemployed, 59% are female, 56% are partnered (married or common law). Of the sample population, 66 % consider themselves in excellent or good mental health while 13% assess their mental health as poor. Overall, young adults between 15 and 34 years old represent 15% of the sample, 57% are between 35 and 64 years, and the 65+ age group is represented by 28% of the sample.

Moreover, Table 1 reveals that there is a difference between the full CPSS6 sample and analytic sample 1 of substantial magnitude with respect to unsuccessful help-seeking for emotions, mental health and substance misuse, self-reported mental health, employment status and marital status. Analytic sample 1 respondents appear to be more likely to seek help, but be unable to find it, compared to the full CPSS6 dataset. They are also more likely to be in poor mental health, unemployed and single, widowed, or divorced. By design of inclusion criteria, analytic sample 1 respondents are all present or past opioid users, and therefore the difference in descriptive statistics with respect to opioid use was expected.

Analytic sample 2: NPD use change during COVID-19: From Table 1, we see that 83% of respondents were born in Canada, 48% hold a university degree, 81% live in urban areas, 38% are unemployed, 52% are female, 51% are partnered (married or common law). Among the analytic sample 2 respondents, 65% of consider themselves in excellent mental health while 12% assess their mental health as poor. Young adults between the age of 15 and 34 represent 22% of the sample, 55% are between 35 and 64 years, and the 65+ age group is represented by 23% of the sample.

We can see that compared to the full CPSS6 sample, analytic sample 2 respondents significantly differ with respect to NPD use change, unsuccessful help-seeking for substance misuse, mental health, marital status, and age. Overall, the respondents are younger, more likely to be single, widowed or divorced, in poor mental health and unable to find help for substance misuse. By design of inclusion criteria, analytic sample 2 respondents are all present or past NPD users, and therefore the difference in descriptive statistics with respect to opioid use was expected.

Analysis

Drug use change and unsuccessful help-seeking

We used a set of four binary logistic regressions within our two separate analytic samples to address our two primary objectives using data from CPSS6 and sample weights. The logistic regressions were estimated as a function of the eight sociodemographic characteristics presented in Table 1. For NPD and opioid use outcomes, we assessed whether consumption was likely to 'increase' as opposed to 'decrease or stay the same'. For help-seeking , the binary outcome was a 'yes' versus 'no', responding to whether the respondents were unsuccessful in finding help for substance misuse or mental health problems. The reference category was 'no'.

Regression results are presented both in graphically using odds ratio forest plots with 95% confidence intervals. A tabular form of the results can be found in Appendix B. Additional separate models for demographic and socioeconomic characteristics for each outcome are included in Supplemental Material (see Appendix C). All data analysis was conducted using R and R Studio, version 1.2.1335.

NPD and opioid use change response/valid skip analysis

We have chosen to conduct an additional binomial logit regression analysis to check for possible systemic differences with regards to our predictor variables between the sample of respondents who reported past drug use and those who previously stated that they have not used drugs in the past (valid skip on our outcome variables of interest). This analysis offers a proxy analysis for determinants of 'no drug use' versus 'any level of drug use'. This is because we expect individuals who have never used opioids or NPD drugs to either skip the question or report that it is not applicable to them, thereby indicating that they used no opioids or NPDs, both before and during the pandemic.

The results from this proxy analysis, however, need to be reported with caution, for two alternative scenarios could have happened; firstly, individuals who use drugs but are not comfortable with sharing this information may have skipped the questions, and secondly, individuals who do not use drugs may have misinterpreted the framing of the question and report that their drug use 'stayed the same', that is, at zero consumption. (see Table 2 below for descriptive statistics related to these

additional samples). From the tables, we can see that there are significant differences between respondents and non-respondents of both opioid and NPD questions with respect to self-reported mental health, marital status, and age.

Table 2: Descriptive Statistics for Opioid and NPD Response/Valid Skip analytic sample (category-specific sample proportions in parentheses)

Independent variables		Opioid use change		NPD use change	
		Valid skip (%)	**Valid survey response (%)**	**Valid skip (%)**	**Valid survey response (%)**
Mental Health	Excellent/Good	2830 (79)	230 (66)	2862 (79)	197 (64)
	Fair	604 (17)	73 (21)	607 (17)	71 (23.2)
	Poor	152 (4)	43 (13)	157 (4)	38 (12.4)
Immigration status	Born in Canada	2959 (83)	299 (86)	3002 (83)	256 (83)
	Landed immigrant	634 (17)	47 (14)	629 (17)	52 (17)
Sex	Male	1665 (46)	142 (41)	1662 (46)	146 (47)
	Female	1928 (54)	204 (59)	1969 (54)	162 (53)
Education level	College or lower	2010 (56)	208 (60)	2058 (57)	161 (52)
	University education	1583 (44)	138 (40)	1573 (43)	147 (48)
Place of residence	Rural	764 (21)	61 (18)	764 (21)	60 (20)
	Urban	2829 (79)	285 (82)	2867 (79)	248 (80)
Employment status	Employed	2115 (59)	180 (52)	2111 (60)	184 (62)
	Unemployed	1390 (41)	153 (48)	1430 (40)	113 (38)
Marital status	Married/Common Law	2283 (64)	194 (56)	2307 (63)	169 (55)
	Single/Widowed/Divorced	1310 (36)	152 (44)	1324 (37)	139 (45)
Age group	15-34	585 (16)	53 (15)	569 (16)	69 (22)
	35-64	2004 (55)	196 (56)	2032 (56)	167 (54)
	65+	1004 (29)	97 (29)	1030 (28)	72 (23)
Total Observations (3,932)		3,586	346	3,626	308

From the descriptive statistics, we can see that those who reported prior opioid and NPD use differ from those who did not in terms of their poorer mental health and higher probability of being single, divorced, or widowed, respectively. Moreover, respondents who reported prior opioid use

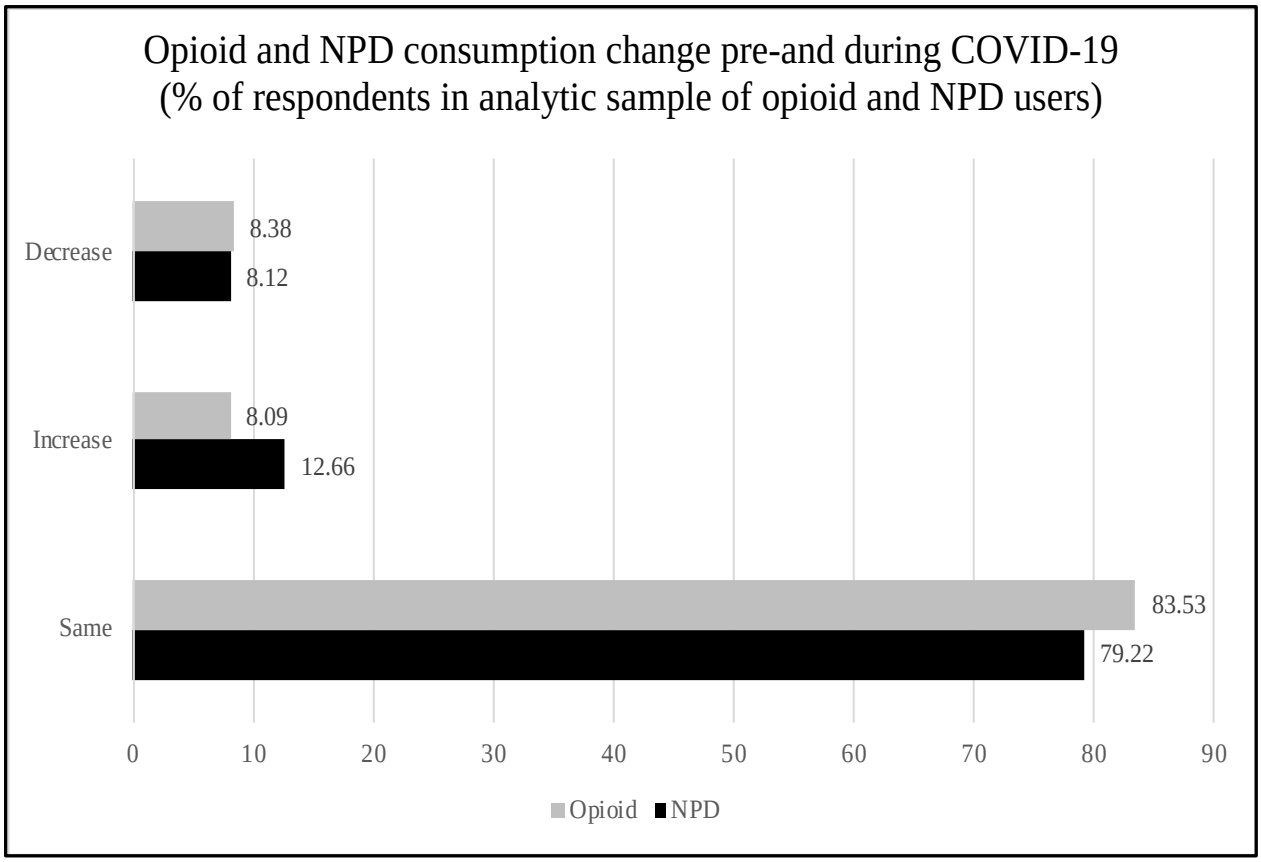
were more likely to be unemployed, while those who reported prior NPD use were younger than those who did not.

Results

Changes in opioid and NPD use pre- and during COVID-19

In the figure below (Figure 1), we see that over 83% of individuals who used opioids before the pandemic did not change their consumption patterns, while roughly 8% of opioid users both increased, and decreased their consumption compared to their pre-pandemic consumption levels. We also see that 79% of individuals who used NPD before the pandemic did not change their consumption patterns, while almost 13% of NPD users increased, and 8% decreased their consumption compared to the pre-pandemic levels. Overall, while roughly 8% of both opioid and NPD user in Canada decreased their consumption during the pandemic, the risk of increased consumption was significantly higher for NPD users than opioid users.

Figure 1: Bar plot of opioid and NPD use change pre and during COVID-19

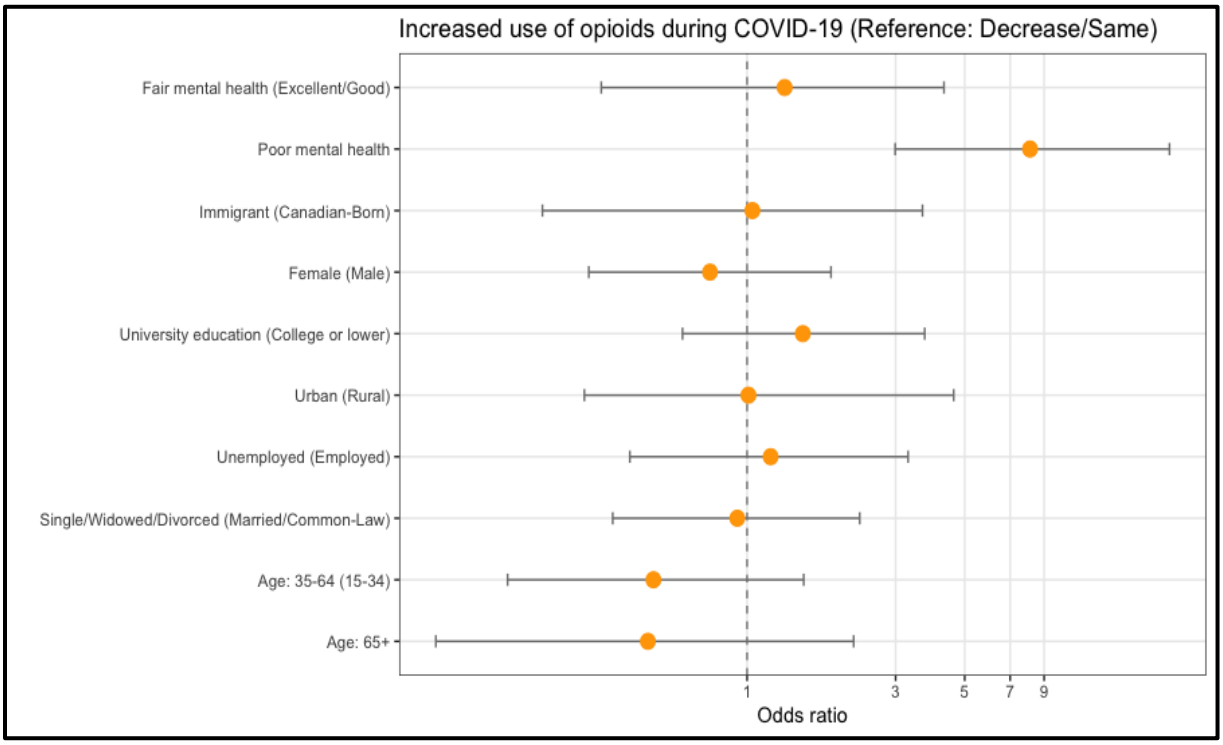


Opioid use increase during COVID-19 and unmet treatment needs for substance misuse and mental health among opioid users

Figures 2 and 3 below presents the associations between opioid use change, ability to access treatment among NPD users and eight predictor variables (binary regression results tables are available in Appendix B).

Odds of opioid use increase - Poor mental health was the only predictor of increased opioid use during the COVID-19 pandemic. Compared to Canadians who self-rated their mental health as excellent or good, those with 'poor' mental health are expected to be 8 times more likely to have increased their opioid use relative to decreasing it or keeping it constant at pre-pandemic levels (8.11, 95% CI 2.99-22.75). We found no effect of immigration, marital and employment status on the odds of increasing opioid consumption. Evidence for the effect of all other included sociodemographic predictors on opioid use increase is inconclusive, given our relatively small sample size (N= 346) and imprecise confidence intervals.

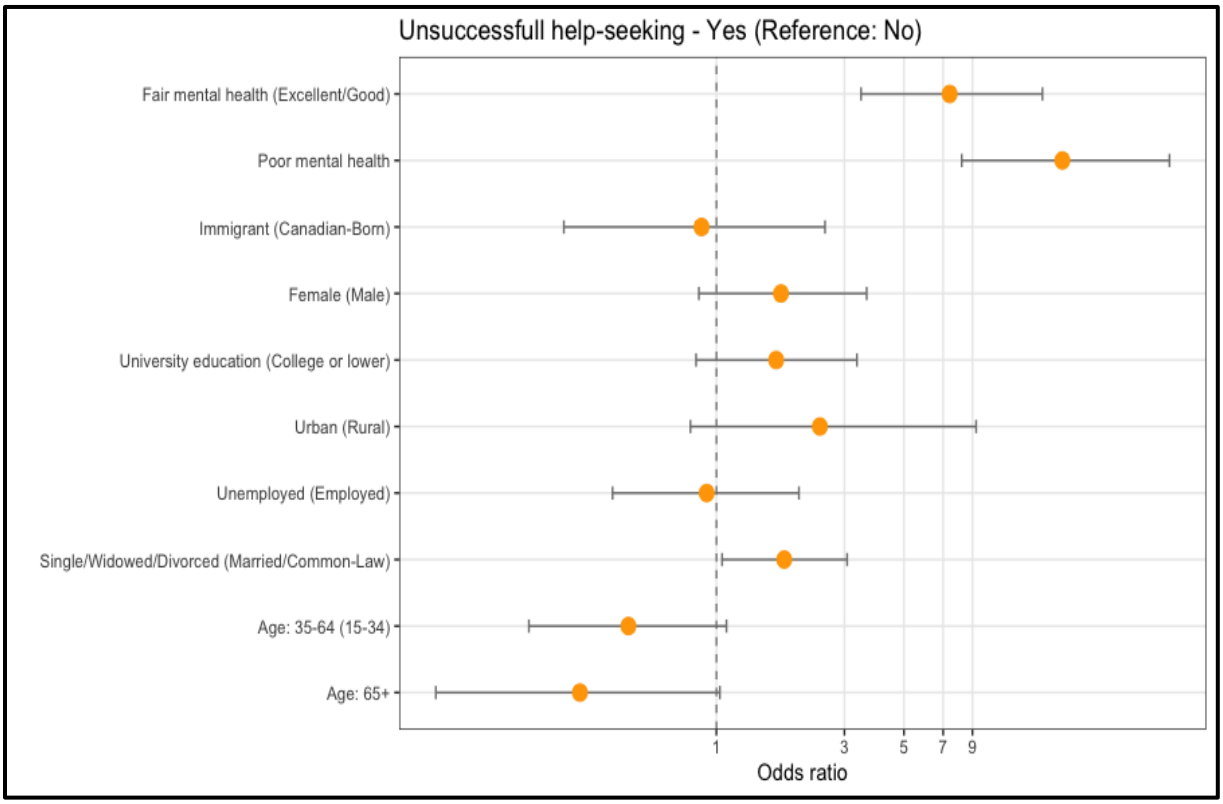
Figure 2: Forest plot of ORs for opioid use increase (compared to decrease/same level of use)



Odds of unmet need for care among opioid users - Our data shows that the odds of seeking help for substance misuse or mental health but being unable to find it follows similar patterns as the

odd of increased opioid use. All else constant, unsuccessful help-seeking, and thereby unmet need for care among opioid users, is strongly associated with fair and poor mental health scores compared to opioid users in excellent or good mental health (Fair: 7.40, 95% CI 3.46-16.41; Poor: 19.48, 95% CI 8.21-48.83). The direction of causality for these associations, however, cannot be determined by this analysis. Further research is needed to explore potential reverse causality and to uncover the actual mechanism behind the relationship between mental health and inability to find satisfactory treatment for misuse. Moreover, single, widowed, or divorced individuals were about 80% more likely to be unsuccessful in seeking help for substance misuse or mental health, compared to their partnered counterparts, keeping all else constant (1.79, 95% CI 1.05-3.07). Our data also shows that older age appears to be a potential protective factor against unmet need. Based on Figure 3, it appears that females, university-educated individuals, and urban dwellers are more likely to be unsuccessful in finding help for substance misuse, compared to males, individuals with college education or lower, and rural dwellers, respectively. No significant difference in the odds of unmet need was observed by immigration status or employment.

Figure 3: Forest plot of ORs for unsuccessful help-seeking for substance misuse and mental health among opioid users (compared to no unsuccessful help-seeking)

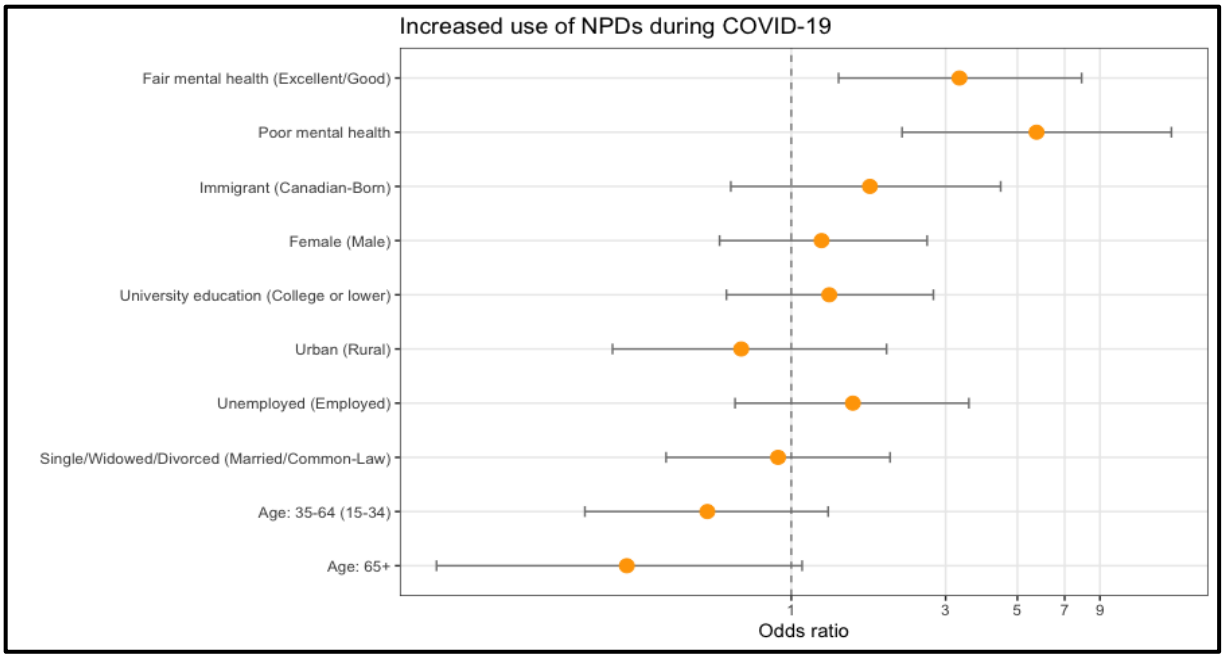


NPD use increase during COVID-19 and unmet treatment needs for substance misuse and mental health among NPD users

Figures 4 and 5 presents the associations between NPD use change, ability to access treatment among NPD users and eight predictor variables (binary regression results tables are available in Appendix B)

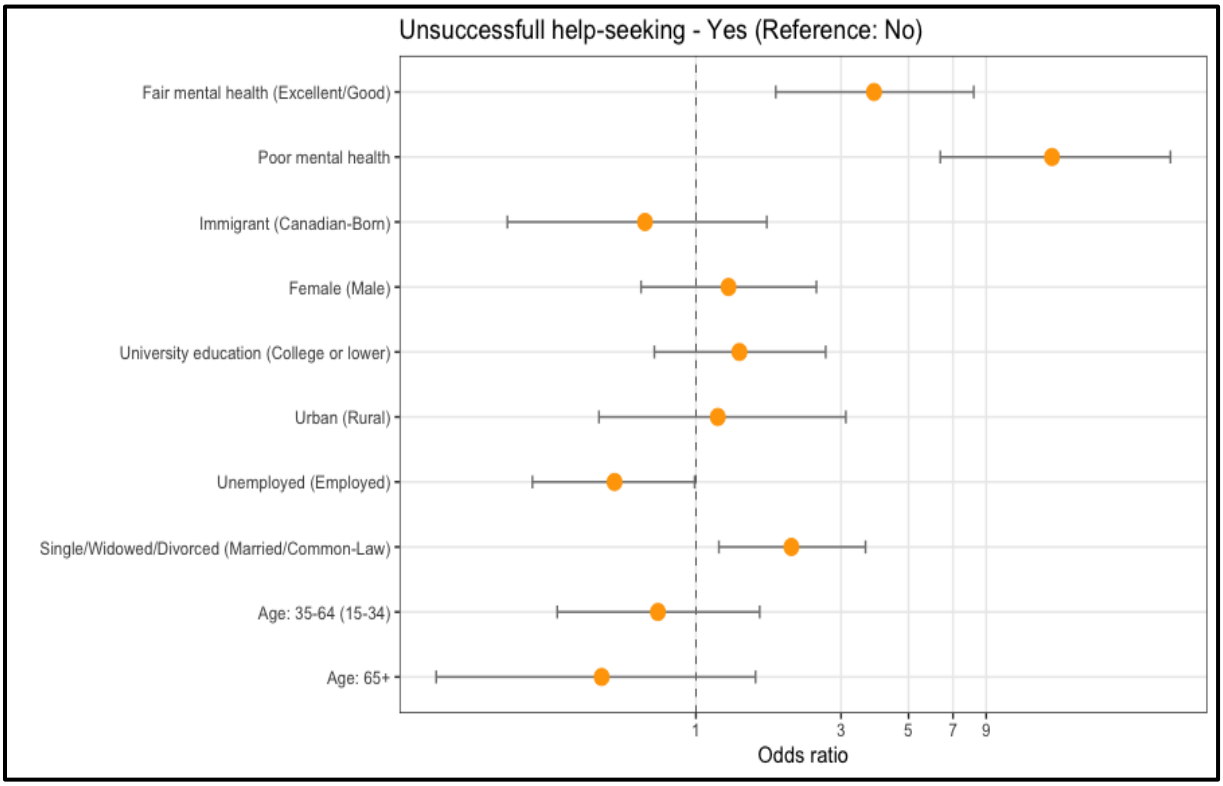
Odds of NPD use increase - Much like with opioid use, we observe that increased use of NPDs during the COVID-19 pandemic is strongly associated with poor mental health. Keeping other covariates constant, compared to Canadians who self-rate their mental health as excellent or good, those with 'fair' and 'poor' mental health respectively are expected to be 3.3 and 5.7 times more likely to have increased their NPD use (Fair: 3.31, 95% CI 1.40-7.90; Poor: 5.73, 95% CI 2.20-14.97). Other predictor variables do not appear to affect the odds of increased NPD use in a statistically significant way, but we nonetheless see age as a potential protective factor. Compared to individuals aged 15 to 36, those over 65 have 70% lower odds of increasing their NPD use, with higher confidence intervals around the null effect (0.31, 95% CI 0.08-1.08). We observed no significant change in drug use patterns by immigration status, sex, education level, place of residence, employment, or marital status.

Figure 4: Forest plot of ORs for NPD use increase (compared to decrease/same level of use)



Odds of unmet need for care among NPD users - Our data shows that the odds of seeking help for substance misuse or mental health but being unable to find it follows similar patterns as the odd of increased NPD use. All else constant, unmet need for care among NPD users is strongly associated with fair and poor mental health scores compared to NPD users in excellent or good mental health (Fair: 3.85, 95% CI 1.83-8.19; Poor: 14.81, 95% CI 6.36-36.31). Additionally, single, widowed, or divorced individuals were about twice as likely to be unsuccessful in seeking help for substance misuse or mental health, compared to their married counterparts, keeping all else constant (2.06, 95% CI: 1.19-3.61). Our data also shows that unemployed individuals are 54% more likely to be able to find help for substance misuse or mental health than employed individuals, all else constant (0.54, 95% CI: 0.29-0.99). No significant difference in the odds of seeking help but being unable to find it was observed by immigration status, sex, education level, place of residence, or age.

Figure 5: Forest plot of ORs for unsuccessful help-seeking for substance misuse and mental health among NPD users (compared to no unsuccessful help-seeking)



Differences between survey respondents who reported past drug use and those who did not

Figures 6 and 7 below, present the results from our binary logit regressions estimating the odds of indicating past opioid and/or NPD drug use (i.e., stating that drug use increased, decreased, or stayed the same) compared to not responding (i.e., validly skipping the questions following a previous response of no recorded use) across our eight predictor variables and unmet need for care (see Appendix B for results tables). This analysis was conducted within our supplemental analytic samples of 3,932 and 3,934 complete cases with respect to our variables of interest, counting valid skip of our outcome variables as a valid response. The results from this analysis could be explained either as differences between respondents and non-respondents, or, when interpreted with caution, proxy results for predictors of drug use compared to no drug use, rather than predictors of response/non-response.

Overall, we observe that individuals with poor mental health scores are more likely to respond to questions related to their drug use, than individuals who self-rate their mental health as excellent or good. The odds of response to drug use questions are over 2.5 times higher for individuals with 'poor' compared to 'excellent' mental health, keeping other variables constant, for opioids (2.74, 95% CI 1.78-4.19) and NPDs (2.53, 95% CI 1.61-3.91), respectively. From Figure 6 and 7, we also see a gradient when it comes to different self-rated mental health scores and both drug use outcomes, whereby as mental health improves, the odds of response to drug questions gradually decrease.

The consistency of these results, especially given the body of existing research evidence of a negative relationship between mental health and substance use, points to the strong possibility that in this case, non-response is not uninformative, and could be used as a proxy for drug use/ non-use. Therefore, our results from proxy analysis suggest that individuals with poor mental health scores are more likely to have a history of drug use that those who self-report excellent mental health.

Figure 6: Forest plot of ORs for opioid use survey response (compared to valid skip)

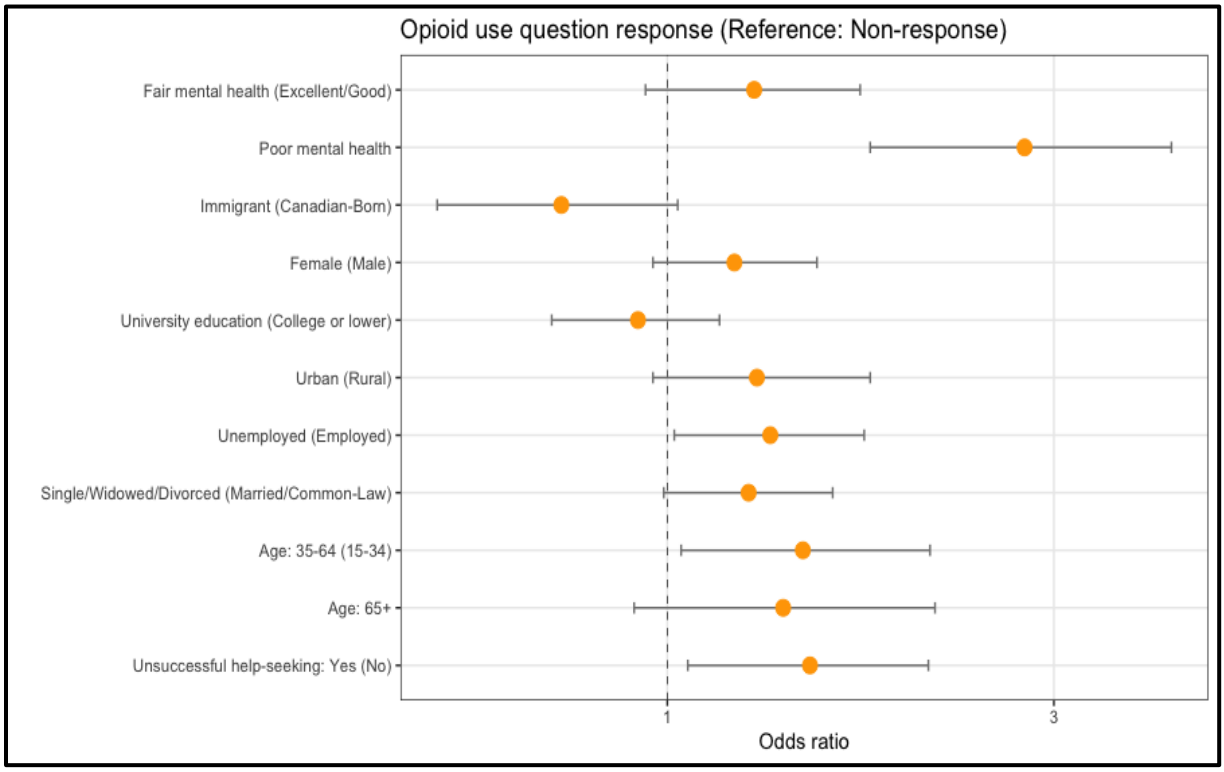
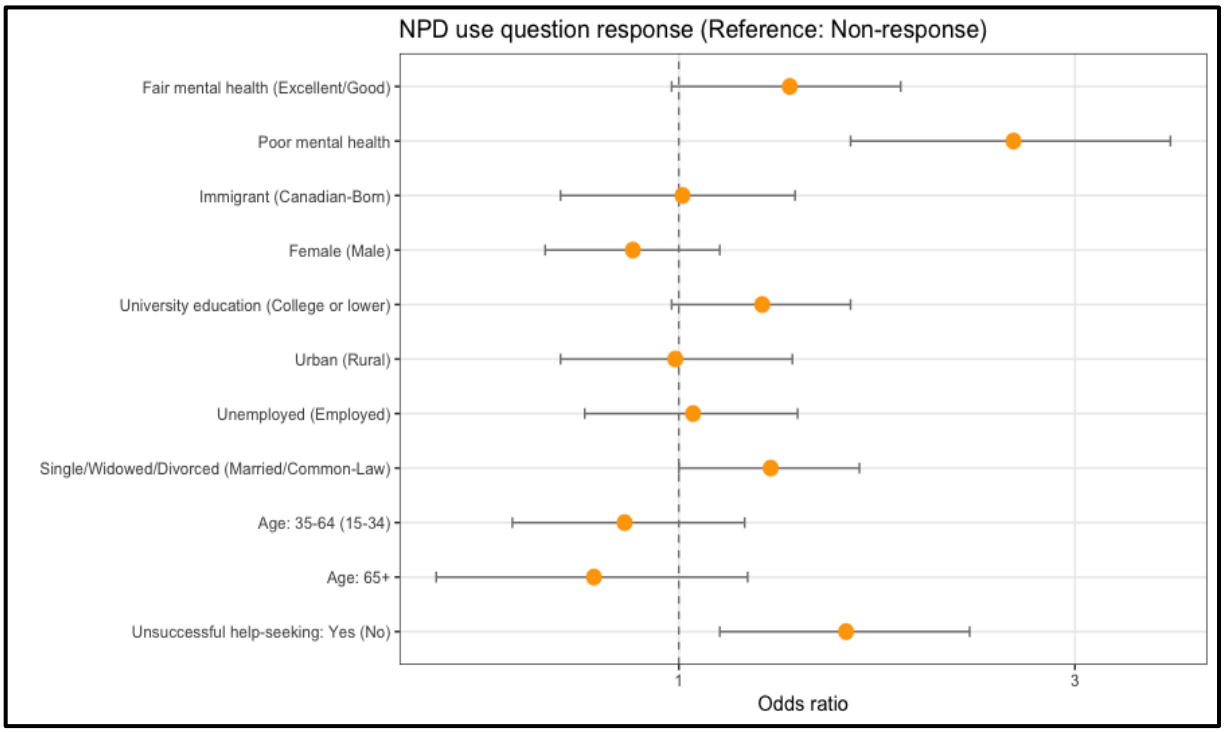


Figure 7: Forest plot of ORs for NPD use survey response (compared to valid skip)



According to our data, single, divorced, or widowed individuals are almost 30% more likely to report opioid and NPD use compared to those who are married or cohabiting with partners, keeping other variables constant (opioids: 1.26, 95% CI 0.99-1.60; NPDs: 1.29, 95% CI 1.00-1.65). Our data also revealed that the odds of responding to opioid use questions were 34% higher for unemployed individuals compared to those who were employed during the COVID-19 pandemic at the time of interview, all else constant (1.35, 95% CI 1.02-1.75). Moreover, the odds of responding to both opioid and NPD use questions were over 50% higher for individuals who stated that they were unable to find needed help for substance use and mental health problems, all else kept constant (Opioids: 1.50, 95% CI 1.06-2.10; NPD: 1.59, 95% CI 1.12-2.24).

Gender, education level, and place of residence do not appear to affect response/nonresponse to both drug use questions in a statistically significant way according to the conventional boundaries of statistical significance at $p<0.05$. However, based on the forest plots (Figure 7 and 8), we observe some trends that may be clinically important, albeit statistically insignificant. Accordingly, the odds of response to NPD use change question are 26% higher for university-educated individuals compared to individuals with a college degree or lower (1.26, 95% CI 0.98-1.61). Similarly, landed immigrants seem to be about 26% less likely to report opioid use than native-born Canadians (0.74, 95% CI 0.52-1.03). We also observe opposing trends in the odds of opioid and NPD use response across age groups. While for opioid use, the odds of response appear to increase with age, for NPD use, the odds tend to decrease.

Discussion

Much of the research published during the initial stages of the COVID-19 pandemic focused on epidemiological modelling, hospitalizations and infection spread directly related to the SARS-COV-2 virus. However, as many indications are now pointing to the fact that we will likely have to learn to live with this virus for at least some years to come, attention must now shift to the consequences of living under the stress and uncertainties of lockdown measures and drastic changes to our lifestyles, work, and public policies.

We are only just starting to uncover the complex impact of the COVID-19 pandemic on mental health, health behaviors and social capital and how these outcomes differ across different sociodemographic characteristics. Vulnerable individuals, such as those with substance use

disorder (SUD) prior to the pandemic, may have been particularly affected by the stress and hardship associated with the sudden lifestyle changes, and increased their drug use as a coping mechanism. Moreover, individuals affected by SUDs were already significantly more likely than the general population comparator to suffer from a myriad of dangerous comorbidities, such as mental health problems, obesity, diabetes, HIV/AIDS as well as unhealthy eating and drinking habits before the pandemic (National Institute on Drug Abuse 2018). Such individuals with co-occurring disorders are also more likely to experience barriers to treatment and access to other integrated resources, while being at higher risk of COVID-19 transmission and worse disease progression. Therefore, the pandemic may have disproportionately affected such individuals in terms of increased substance use, as well as a potential deterioration of other comorbidities.

This paper offers a first glance at opioid and non-prescription drug use pattern changes during the COVID-19 pandemic in Canada. We explored (a) the extent to which opioid and NPD use changed during the pandemic, and (b) whether individuals experienced barriers to access of substance misuse or mental health services. Mapping the changes in drug use, an avoidable risk factor in Canada, as well as the extent of unmet need for mental health and substance abuse services during the pandemic is crucial for effective and evidence-based design of future policy reforms.

Our findings indicate a very strong relationship between poor mental health and co-occurring increasing drug use and inability to find help for substance misuse or mental health. These results not only confirm existing research documenting strong evidence of mental health and substance use comorbidity risk as well as stigma around addiction and unmet needs for treatment in Canada (Urbanoski, Inglis, and Veldhuizen 2017), but also complement emerging studies and reports about negative changes in health behaviors and mental health of Canadians during COVID-19 (Zajacova et al. 2020, Gilmour 2020, Rotermann 2020). The results highlight the need to improve access to integrated services for those who suffer from comorbid substance use and mental health problems, such as depression or suicidal thoughts. It is difficult, however, to establish the causal pathway of our findings (i.e., whether adverse mental health led to increased substance use, whether increased substance use led to poor mental health or whether a common third factor, such as trauma contributed to both).

Another crucial finding was that single, divorced, or widowed individuals were more likely to face unmet needs for care than their married or cohabiting counterparts. They were also significantly more likely to respond to both opioid and NPD consumption change questions, rather than skip the question following a response of 'no drug use' in a previous question. When interpreting this predictor of response as a predictor of drug use, the results are in line with recent research in the field, pointing to increased risk of drug use and loneliness among young and single individuals during the COVID-19 pandemic (Horigian et al. 2021). Single individuals may have been unable to date and socialize with friends, which may naturally lead to loneliness, mental health problems and potentially drug use as a coping mechanism. This highlights the vast potential importance of social contact, intimacy, and physical company, all of which single individuals were deprived of during more than a year of confinement. The relationship between loneliness, mental health and substance use has already been documented in research prior to the pandemic, but the risks of drug use and abuse associated with these factors are even more pressing now (Horigian et al. 2021).

We found no statistically significant evidence of a sex effect in drug use change, but females do appear to report more difficulties accessing services for substance misuse, despite seeking help. This points to the need to design substance use interventions with gender in mind and sensitive to a potentially differential level of stigma associated with drug use for females, compared to males, which may lead to differential help-seeking behavior by gender. No positive unemployment effect was found for an increase in either in drug use during COVID-19 or help-seeking behavior. In fact, unemployed NPD-using individuals appeared less likely to face unmet needs for substance misuse and mental health treatment than their employed counterparts.

While older age appears to be a protective factor against an increase in consumption of both opioids and NPDs during the COVID-19 pandemic, as well as unmet needs in both populations, we observed opposing trends in the odds of opioid and NPD use question response across age groups. While for opioid use, the odds of response appear to increase with age, for NPD use, the odds decrease. This suggests that two separate opioid and NPD use trends may be at play. While older individuals may be at higher risk for misuse of opioids, as a potential coping mechanism with increasing discomfort and chronic pain associated with aging, NPD use may be more concentrated

among younger age groups, to cope with life-related stressors, such as education, financing, and work-family balance.

The findings presented from our analysis are limited by the cross-sectional design of the CPSS data series. We are only able to present a snapshot of a specific time period in the Canadian experience of the pandemic, rather than uncover longitudinal trends over the period of the pandemic and prior to it. Furthermore, due to space and scope limitations, we chose to limit our analysis to an exploration of the risk factors associated with increased drug consumption during the COVID-19 pandemic. Investigation of potential protective factors associated with decreased drug use is also substantially important to the community of researchers and decision makers and should be addressed in future studies.

An additional potential limitation of our analysis is that all our outcomes of interest were subject to potential recall bias and incorrect assessment of individual changes in drug use at the time of the interview. Moreover, we cannot assess the magnitude of the self-reported, subjective changes. Similarly, without follow-up, we are unable to establish the proportion of individuals who have previously not consumed any drugs and initiated consumption only during the COVID-19 pandemic. This makes it difficult to uncover the precise mechanisms through which the changes in drug use occurred, and individual characteristics that contribute to increased risk of initiating drug consumption. Likewise, we are unable to uncover if, and how were mental health outcomes affected as the pandemic progressed. There are also notable limitations related to the risk of bias. Although reporting bias and social desirability bias appear to be a serious possibility for all ages due to the sensitive nature of the subject, the survey respondents are assured that their responses will remain secure, confidential, and anonymous. Moreover, due to a relatively high non-response rate to CPSS6 survey among CPSS panelists (46.6%), it is likely that those who volunteered to respond differ in meaningful ways from those who did not, which may result in selection bias.

Another issue pertains to the wording of the opioid question, which includes both prescribed and non-prescribed opioids, precluding a differentiated analysis of legal and illicit consumption change patterns, which may well have differed during the pandemic. Due to the phrasing of the survey question, however, it is also possible that many respondents incorrectly stated that they have never

used opioids if they were unaware that this category also included prescribed and non-prescribed opioids such as OxyContin, Codeine, or Tylenol 1, 2, 3 or 4. While the questionnaire provided an explanatory list of the description of included drugs, some respondents may have skipped the explanation, unsuspecting that some opioids are legal and commonly prescribed for severe pain management. It was very interesting in this context to find overwhelmingly similar associations between our sociodemographic determinants and both outcomes, (licit or illicit) opioid use change and illicit NPD use change.

Further, data availability posed additional challenges for our analysis and the robustness of our results. For example, variables related to ethnicity, indigenous status, homelessness, and province of residence were not available as part of the CPSS 6 data series. Moreover, the reported variable for sex of respondents is dichotomized into 'male' and 'female' only, leaving individuals who do not identify with either of these categories invisible. These covariables would have been a valuable addition to our regression analyses, for they would allow us to control for a well-documental differential impact of COVID-19 among different ethnic groups (Rentsch et al. 2020), vulnerable groups, such as homeless individuals (Perri, Dosani, and Hwang 2020) or gender/sexual minorities (Parent et al. 2018), and differential burden of the pandemic across different Canadian provinces (Detsky and Bogoch 2020). We appreciate the difficulties in designing surveys such as CPSS, but would welcome if future waves collected more equity, diversity and inclusion variables and presented them as part of their PUMF datasets.

Conclusion

This paper explored the extent to which COVID-19 affected opioid and NPD use among Canadians and examined their help-seeking behavior for substance misuse or mental health, controlling for a range of sociodemographic determinants. We document significant associations between perceived mental health and increased drug use, as well as an inability to access substance misuse or mental health resources. This highlights the importance of providing enhanced integrated services for mental health and substance abuse comorbidities in Canada. As we slowly emerge from the pandemic thanks to successful containment policies and vaccination campaigns, we should start considering how to provide needed support and tailored interventions to address additional consequences of the COVID-19 pandemic, the stress, isolation, uncertainty, and changes to our daily lives and lifestyles, such as changes to drug use, among other health behaviors.

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Appendix A:
Relevant parts of the Questionnaire

Substance use – opioids (OPI)

OPI_BEG External Variables required:

OPI_Q05 The following questions are about your opioid use.
In the past 30 days, have you used any prescribed or non-prescribed drugs containing opioids?

ON-SCREEN HELP: By opioids, we mean products such as codeine, oxycodone, OxyContin, OxyNeo, hydromorphone, Dilaudid, morphine, fentanyl, methadone, Tylenol 1, 2, 3 or 4, 292s, Robaxacet-8, Percocet, Percodan, Demerol, AC&C, Mersyndol, Calmylin, and heroin for either medical or non-medical purposes.

1 Yes
2 No, not during the past 30 days
3 Never used opioid products
(Don't know, Refusal not allowed)

OPI_C10 If OPI_Q05 = 3, go to OPI_END.
Otherwise, go to OPI_Q10.

OPI_Q10 On average, over the course of the COVID-19 pandemic, how has your use of opioids changed when comparing to **before** the pandemic?

1 Increased
2 Decreased
3 Not applicable
4 Stayed about the same
(Don't know, Refusal not allowed)

Substance use – non-prescribed drugs (NPD)

NPD_BEG External Variables required:

NPD_Q05 The following questions are about your non-prescribed drug use.
In the past 30 days, did you use any non-prescribed drugs?

ON-SCREEN HELP: **Exclude** cannabis and opioids.
For the purpose of this survey, non-prescribed drugs refer to the use of various substances, such as cocaine, crystal meth, amphetamines, ecstasy, hallucinogens, as well as the misuse of over-the-counter drugs.
By "misuse of over-the-counter drugs", we mean **for example**, for the purpose of getting high, use of laxatives for weight loss, taking higher than recommended doses, **etc.**

1 Yes
2 No, not during the past 30 days
3 Never used any non-prescribed drugs
(Don't know, Refusal not allowed)

NPD_C10 If NPD_Q05 = 3, go to NPD_END.
Otherwise, go to NPD_Q10.

NPD_Q10 On average, over the course of the COVID-19 pandemic, how has your use of non-prescribed drugs changed when comparing to **before** the pandemic?

1 Increased
2 Decreased
3 Not applicable
4 Stayed about the same
(Don't know, Refusal not allowed)

HS_Q20 Since the beginning of the COVID-19 pandemic, was there ever a time when you felt that you needed help for your emotions, mental health or use of alcohol or drugs, but you didn't receive it?

ON-SCREEN HELP: **Include** alcohol and prescribed and non-prescribed drugs.

1 Yes
2 No
(Don't know, Refusal not allowed)

HS_END

Appendix B:
Binomial regression analyses

Binomial logistic regressions of opioid use changes and ability of opioid users to access help

Independent variables		OR (Opioid use increase) Reference: decrease/same	OR (unsuccessful help-seeking- yes), Reference: no
Mental Health	Excellent/Good	(reference)	(reference)
	Fair	1.32 (0.34-4.29, p=0.660)	7.40 (3.46-16.41, p<0.001)
	Poor	8.11 (2.99-22.75, p<0.001)	19.48 (8.21-48.83, p<0.001)
Immigration status	Born in Canada	(reference)	(reference)
	Landed immigrant	1.04 (0.22-3.66, p=0.952)	0.88 (0.27-2.54, p=0.825)
Sex	Male	(reference)	(reference)
	Female	0.76 (0.31-1.86, p=0.541)	1.74 (0.86-3.63, p=0.127)
Education level	College or lower	(reference)	(reference)
	University education	1.51 (0.62-3.72, p=0.364)	1.67 (0.84-3.34, p=0.144)
Place of residence	Rural	(reference)	(reference)
	Urban	1.01 (0.30-4.61, p=0.987)	2.43 (0.80-9.29, p=0.147)
Employment status	Employed	(reference)	(reference)
	Unemployed	1.19 (0.42-3.29, p=0.733)	0.92 (0.41-2.03, p=0.846)
Marital status	Married/Common Law	(reference)	(reference)
	Single/Widowed/Divorced	0.93 (0.37-2.30, p=0.882)	1.79 (1.05-3.07, p=0.033)
Age group	15-34	(reference)	(reference)
	35-64	0.50 (0.17-1.52, p=0.202)	0.47 (0.20-1.09, p=0.075)
	65+	0.48 (0.10-2.20, p=0.348)	0.31 (0.09-1.03, p=0.059)
Observations:			346

Binomial logistic regressions of NPD use changes and ability of NPD users to access help

Independent variables		OR (NPD use increase) Reference: decrease/same	OR (unsuccessful help-seeking- yes) Reference: No
Mental Health	Excellent/Good	(reference)	(reference)
	Fair	3.31 (1.40-7.90, p=0.006)	3.85 (1.83-8.19, p<0.001)
	Poor	5.73 (2.20-14.97, p<0.001)	14.81 (6.36-36.31, p<0.001)
Immigration status	Born in Canada	(reference)	(reference)
	Landed immigrant	1.75 (0.65-4.44, p=0.247)	0.68 (0.24-1.71, p=0.430)
Sex	Male	(reference)	(reference)
	Female	1.24 (0.60-2.63, p=0.565)	1.28 (0.66-2.49, p=0.469)
Education level	College or lower	(reference)	(reference)
	University education	1.31 (0.63-2.75, p=0.471)	1.39 (0.73-2.67, p=0.321)
Place of residence	Rural	(reference)	(reference)
	Urban	0.70 (0.28-1.97, p=0.478)	1.18 (0.48-3.11, p=0.724)
Employment status	Employed	(reference)	(reference)
	Unemployed	1.55 (0.67-3.54, p=0.300)	0.54 (0.29-0.99, p=0.051)
Marital status	Married/Common Law	(reference)	(reference)
	Single/Widowed/Divorced	0.91 (0.41-2.02, p=0.823)	2.06 (1.19-3.61, p=0.011)
Age group	15-34	(reference)	(reference)
	35-64	0.55 (0.23-1.30, p=0.166)	0.75 (0.35-1.62, p=0.455)
	65+	0.31 (0.08-1.08, p=0.075)	0.49 (0.14-1.57, p=0.239)
Observations:			308

Binomial logistic regressions of opioid and NPD question response

Independent variables		OR (Opioid use response) Reference: valid skip/not applicable	OR (NPD use response) Reference: valid skip/not applicable
Mental Health	Excellent/Good	(reference)	(reference)
	Fair	1.28 (0.94-1.73, p=0.116)	1.36 (0.98-1.85, p=0.060)
	Poor	2.76 (1.78-4.19, p<0.001)	2.53 (1.61-3.91, p<0.001)
Immigration status	Born in Canada	(reference)	(reference)
	Landed immigrant	0.74 (0.52-1.03, p=0.079)	1.01 (0.72-1.38, p=0.965)
Sex	Male	(reference)	(reference)
	Female	1.21 (0.96-1.53, p=0.114)	0.88 (0.69-1.12, p=0.290)
Education level	College or lower	(reference)	(reference)
	University education	0.92 (0.72-1.16, p=0.468)	1.26 (0.98-1.61, p=0.070)
Place of residence	Rural	(reference)	(reference)
	Urban	1.29 (0.96-1.78, p=0.102)	0.99 (0.72-1.37, p=0.948)
Employment status	Employed	(reference)	(reference)
	Unemployed	1.34 (1.02-1.75, p=0.035)	1.04 (0.77-1.39, p=0.800)
Marital status	Married/Common Law	(reference)	(reference)
	Single/Widowed/Divorced	1.26 (0.99-1.60, p=0.055)	1.29 (1.00-1.65, p=0.049)
Age group	15-34	(reference)	(reference)
	35-64	1.47 (1.04-2.11, p=0.033)	0.86 (0.63-1.20, p=0.363)
	65+	1.39 (0.91-2.14, p=0.136)	0.79 (0.51-1.21, p=0.269)
Unsuccessful help-seeking	No	(reference)	(reference)
	Yes	1.50 (1.06-2.10, p=0.021)	1.59 (1.12-2.24, p=0.009)
Observations:		3,932	3,934

Appendix C:

Supplemental binomial logistic models (subgroup analyses)

Demographic variables		OR (Opioid use increase), Reference: decrease/same	OR (unsuccessful help-seeking-yes), Reference: no
Immigration status	Born in Canada	(reference)	(reference)
	Landed immigrant	1.06 (0.43-2.39, p=0.886)	0.68 (0.24-1.65, p=0.424)
Sex	Male	(reference)	(reference)
	Female	0.67 (0.38-1.19, p=0.173)	1.49 (0.84-2.70, p=0.174)
Place of residence	Rural	(reference)	(reference)
	Urban	1.32 (0.61-3.18, p=0.506)	2.13 (0.94-5.49, p=0.088)
Age group	15-34	(reference)	(reference)
	35-64	0.70 (0.33-1.56, p=0.362)	0.33 (0.17-0.65, p=0.001)
	65+	0.69 (0.28-1.70, p=0.408)	0.16 (0.06-0.39, p<0.001)
Observations:			346

Socio-economic variables		OR (Opioid use increase), Reference: decrease/same	OR (unsuccessful help-seeking-yes), Reference: no
Mental health	Excellent/Good	(reference)	(reference)
	Fair	1.40 (0.37-4.43, p=0.590)	8.32 (3.97-18.06, p<0.001)
	Poor	9.07 (3.56-23.74, p<0.001)	22.86 (10.01-55.22, p<0.001)
Education level	College or lower	(reference)	(reference)
	University education	1.37 (0.57-3.28, p=0.474)	1.73 (0.90-3.39, p=0.103)
Employment status	Employed	(reference)	(reference)
	Unemployed	1.02 (0.42-2.44, p=0.963)	0.72 (0.37-1.38, p=0.323)
Marital status	Married/Common Law	(reference)	(reference)
	Single/Widowed/Divorced	0.98 (0.40-2.31, p=0.958)	1.15 (0.60-2.21, p=0.672)
Observations:			346

Demographic variables		OR (NPD use increase), Reference: decrease/same	OR (unsuccessful help-seeking- yes), Reference: no
Immigration status	Born in Canada	(reference)	(reference)
	Landed immigrant	1.84 (0.87-3.79, p=0.104)	0.58 (0.22-1.33, p=0.226)
Sex	Male	(reference)	(reference)
	Female	0.83 (0.47-1.48, p=0.530)	1.35 (0.77-2.40, p=0.295)
Place of residence	Rural	(reference)	(reference)
	Urban	1.09 (0.51-2.49, p=0.829)	1.20 (0.58-2.65, p=0.632)
Age group	15-34	(reference)	(reference)
	35-64	0.34 (0.18-0.64, p=0.001)	0.60 (0.32-1.13, p=0.108)
	65+	0.19 (0.07-0.46, p<0.001)	0.20 (0.07-0.50, p=0.001)
Observations:			308

Socio-economic variables		OR (NPD use increase), Reference: decrease/same	OR (unsuccessful help-seeking- yes), Reference: no
Mental health	Excellent/Good	(reference)	(reference)
	Fair	3.97 (1.72-9.27, p=0.001)	4.32 (2.09-9.03, p<0.001)
	Poor	6.37 (2.51-16.19, p<0.001)	16.23 (7.08-39.14, p<0.001)
Education level	College or lower	(reference)	(reference)
	University education	1.29 (0.63-2.68, p=0.491)	1.35 (0.71-2.58, p=0.362)
Employment status	Employed	(reference)	(reference)
	Unemployed	1.29 (0.61-2.70, p=0.503)	0.64 (0.31-1.26, p=0.206)
Marital status	Married/Common Law	(reference)	(reference)
	Single/Widowed/Divorced	0.89 (0.43-1.84, p=0.760)	1.37 (0.72-2.60, p=0.342)
Observations:			308

Chapter 5: Discussion

Preface

In this chapter, I provide a summary of findings from the thesis and their relevance for policy development and future research. I also briefly discuss the strengths and limitations of my methodological approaches and data sources. Lastly, I offer concluding remarks.

Summary of findings

In my literature review (Chapter 2), I provided a brief overview of the theoretical debates on policy design types and how they relate to the distribution of health outcomes across the population. I found that the existing debate, while extensive, is unable to provide a clear and unambiguous conceptualization of an equitable policy framework to curb illicit drug use across all population strata. In my subsection '*Illicit drug use, subpopulations, and disparities'*, I presented an overview of recent research on the distribution of the overall burden of problematic illicit drug use and related comorbidities. The overview demonstrated the existence of persistent and well-documented socio-demographic disparities in health outcomes related to illicit drug use, as well as associated comorbidities on a global scale.

To categorize different domains of disadvantage associated with unfair differences in population-level illicit drug use burden and access to available services, I used the PROGRESS-Plus classificatory framework for socially stratifying factors of health outcomes. Apart from providing research evidence for inclusion of the original PROGRESS domains, I have identified and included 4 additional disadvantage domains, namely age, disabilities and comorbidities, substance use disorders and time-dependent life events. Lastly, I provided a brief review of the current state of evidence for the impact of the COVID-19 pandemic on the existing distribution of illicit drug use and disadvantage across the previously identified PROGRESS-Plus subpopulations at-risk. I found evidence for an increased disadvantage among subpopulations at-risk during the pandemic, such as a growing anti-Asian sentiment or educational disruptions for the most socio-demographically deprived members of the society. I also noted the emerging trends in recent research on illicit drug use changes during the COVID-19 pandemic among PROGRESS-Plus subpopulations. The general trend shows that overall, for most subpopulations examined, drug use prevalence decreased, but frequency of use increased, pointing to the growing risks of social isolation and stress borne by disadvantaged individuals who already used substances prior to the COVID-19 pandemic.

In Manuscript 1, (Chapter 3) I used umbrella review methodology to shed light on the representation of PROGRESS-Plus subpopulations in systematic reviews and meta-analyses evaluating the effectiveness of illicit drug policy interventions. I found evidence pointing to

underrepresentation of individuals with low occupational prestige and socioeconomic status, low educational attainment, social capital, and religious minorities in impactful knowledge syntheses. Given the status of systematic reviews as 'best available evidence' for decision makers, such a gap in subpopulation representation may affect both their understanding of the health equity impact of the existing interventions and ability to respond to a potential differential effectiveness across these unexamined subpopulations.

Among the PROGRESS-Plus subpopulations that were represented in systematic reviews, most reviews looked at targeted interventions for the specific subgroups analyzed, such as school-based interventions for children and adolescents, or cultural intervention adaptations for indigenous populations. The findings generally point to their effectiveness in reducing or preventing illicit drug use among these subpopulations. Fewer reviews looked at how universal interventions affect subpopulations and the evidence for their effectiveness across these subpopulations was generally either positive or mixed. The initial results provided by our manuscript point to the strengths of targeted universalism and therefore to supplementing large, widely accessible illicit drug interventions, such as mass media campaigns or community outreach programs, with additional targeted services for individuals at increased risk of illicit drug use and associated adverse health outcomes. Overall, the findings suggest the need for further research into the effectiveness of universal interventions across all PROGRESS-Plus subpopulations, as well as new systematic reviews of effective subpopulation-specific illicit drug interventions.

In my second manuscript, presented in Chapter 4, I used data from Statistics Canada to quantitatively examine population characteristics associated with changes in opioid and non-prescription drug (NPD) use frequency during the COVID-19 pandemic in Canada. As a second objective, I examined socio-demographic characteristics associated with barriers to resources and assessing help for substance misuse or mental health. Using a set of binary logistic regression analyses, I found a significant negative association between self-reported mental health and changes in opioid and NPD use during the pandemic. Compared to individuals with excellent mental health, those with poor mental health were over five times more likely to have increased their consumption of opioids and NPDs over the course of the pandemic. When it came to help-seeking behavior, poor mental health was also significantly associated with inability to find and

access help. Moreover, I found that single, divorced, or widowed individuals were more likely to seek help for substance misuse and mental health, but remain unable to find it, compared to their married or cohabiting counterparts. These results conform with the extensive research evidence pointing to a strong and established relationship between the risk of both licit and illicit drug use, adverse mental health outcomes, loneliness, and lack of community network, all of which may have been severely negatively affected during the COVID-19 pandemic.

The findings from Manuscript 2 point to the relevance of multiple PROGRESS-Plus factors, namely social capital, and mental health comorbidities, as determinants of disadvantage in the Canadian population. In the context of our analysis, we found no statistically significant differences in opioid and non-prescription drug use change during the pandemic or inability to find help by education, occupation, and age as disadvantage factors. However, due to data limitations, we were unable to assess associations for eight PROGRESS-Plus domains: race/ethnicity, sexual orientation, religion, socioeconomic status, pre-existing disabilities and substance use disorders or relevant time-dependent life events, such as a recent release from prison, or a death of a loved one. Future research should attempt to include these domains to address the gaps in our current understanding of the effect of the COVID-19 pandemic and associated lockdown measures on subpopulation-specific changes in drug use and ability to access valuable resources.

Strengths

By including specific 'plus' disadvantage factors relevant to the risks associated with illicit drug use, my thesis applied and adapted the PROGRESS-Plus Equity Framework to research on illicit drug use. To my knowledge, it is the first study with an objective to systematically review existing reviews for representation of disadvantaged subpopulations at increased risk of harmful illicit drug use. The findings have important implications for future systematic intervention evaluation reviews, highlighting the need for inclusion of subpopulations in evaluation. Apart from that, my study offers a ready-to-use PROGRESS-Plus framework adapted for illicit drug use to quickly identify domains of potential disadvantage that need to be addressed in future intervention evaluations of any design.

The relevance of examining illicit drug use and associated health equity concerns was ever-important in the context of the ongoing COVID-19 pandemic and my study offers relevant and timely insights into the impacts of the pandemic on changes in opioid and NPD use. The dataset I used in my analytic manuscript (Chapter 4) was published by Statistics Canada in March 2021, and so an additional strength of my thesis is its aptness and rapid contribution to the much-needed evidence on the large scale and unevenly distributed social and health impacts of the pandemic.

Limitations and directions for future research

While my thesis attempted to address important gaps in our understanding of the subpopulation representation in systematic reviews and characteristics associated with illicit drug use change during the pandemic, it nonetheless contains methodological constraints and several limitations for causal inferences.

The topic of illicit drug use policy evaluation has been addressed in a large quantity of systematic reviews, and given limited time and resources, it was impossible to review all existing systematic reviews that mention effectiveness of illicit drug use interventions and determine the proportion of them with subpopulation evaluation. Instead, I solely concentrated my search strategy on reviews that explicitly addressed PROGRESS-Plus subpopulations and mentioned subpopulation-specific findings in their titles or abstracts. This means that there may be unidentified systematic reviews that addressed relevant subpopulation characteristics, but were missed in my umbrella review, thereby biasing my conclusions about representation of subpopulations. To further contribute to the topic, future researchers should aim to conduct scoping reviews of subpopulation representation in primary studies. This would allow us to better understand whether the PROGRESS-Plus disadvantage domains I identified as underrepresented in systematic reviews are also missing in primary intervention evaluations, or whether this is an issue specifically pertaining to the knowledge syntheses.

Similarly, another frontier to consider in future research lies in the intersection of the individual PROGRESS-Plus domains, for as I pointed out in Manuscript 1, a significant limitation of the framework lies in its inability to provide an unambiguous, mutually exclusive, and collectively exhaustive list of disadvantage factors. Although beyond the scope of this thesis, further

understanding and conceptual differentiation of how different PROGRESS-Plus domains interact, affect, and intersect with each other, may provide valuable contribution to the research field.

It may also be beneficial to investigate potential publication bias in primary studies, such as by checking research registries for unpublished papers that may have had insignificant or null findings and were therefore discontinued. For example, it may be possible that illicit drug intervention effectiveness for unemployed and vulnerably employed individuals may differ from the general population comparator in an important way, and yet the association may fail to meet the traditional threshold for statistical significance, potentially contributing to publication bias in the field.

Future research should also aim to determine whether similar studies are being conducted in low and middle-income countries (LMIC) or whether it is possible to translate the knowledge from existing studies conducted in high-income OECD countries to LMIC.

I used a very broad definition of illicit drug use as my outcome variable of interest. As a result, the findings from my umbrella review cannot be synthesized into specific guidelines of equity-conscious and effective interventions for decision-makers. Future research might consider stratifying it into its respective subcategories, for a more focused and guided set of policy recommendations.

In my second manuscript, I provided a timely regression analysis using a recent Statistics Canada CPSS6 PUMP dataset. However, the dataset provided cross-sectional survey data only, and therefore offered us a limited snapshot of a specific time period, rather than longitudinal trends. Use of such datasets, and specifically relying on survey respondents' subjective assessment of longitudinal trends, such as the self-perceived change in drug use pre- and during the COVID-19 pandemic, is inherently flawed and prone to recall bias. Moreover, since the main outcome variable of interest for opioid use change included both prescribed and non-prescribed opioids, we could not distinguish between changes in licit and illicit opioid use in this analysis. However, the associations between our sociodemographic determinants and opioid use change were overwhelmingly similar to those of NPD use change. While this could be due to a misinterpretation of the question by respondents (who may be unaware that certain categories of opioids are legally

prescribed), it could also suggest that similar factors are at play with changes in both illicit drug use and prescription drugs for pain management during the COVID-19 pandemic in Canada. Finally, given the sensitivity of the topic and stigma associated with illicit drug use, there is a strong potential for non-response bias and social desirability bias, despite the significant emphasis that Statistics Canada places on anonymity and non-traceability of survey respondents.

Notwithstanding these limitations, the cross-sectional survey dataset offered me a valuable opportunity to rapidly respond and contribute to our current and much-needed understanding of the population characteristics associated with changes in drug use during the COVID-19 pandemic in Canada. I hope that future researchers may profit from fuller, longitudinal datasets with variables that are currently missing from the CPSS6, such as ethnicity or sexual orientation.

Conclusions

This thesis improved our understanding of the PROGRESS-Plus subpopulation representation in illicit drug intervention evaluation syntheses and pointed to the need for more systematic reviews that evaluate universal illicit drug interventions for individuals with any PROGRESS-Plus disadvantage characteristics, but especially vulnerable occupational status, religious minority status, low educational attainment, social capital, and socioeconomic status. Specific disadvantage domains, such as mental health comorbidities, were also found significantly associated with increased licit and illicit drug use and inability to access misuse services during the COVID-19 pandemic in Canada. Subgroup-specific findings from my umbrella review point to the effectiveness of integrated services for substance use and mental health targeted at individuals with dual diagnosis. In the light of the preliminary findings from this thesis, decision-makers in Canada and elsewhere may consider expanding and improving upon such integrated services to respond to the growing co-occurrence of stress, mental exhaustion, depression, and drug use as a result of the COVID-19 pandemic.

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