Title: The health impact of social exclusion: a systematic review and meta-analysis of morbidity and mortality data from homeless, prison, sex work and substance use disorder populations in high-income countries.

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Abstract

Background:

Inclusion health focuses on people in extremes of poor health due to poverty, marginalisation and multiple morbidity. We aimed to synthesise morbidity and mortality data on overlapping populations experiencing deep social exclusion evident by homelessness, substance use disorders, sex work and imprisonment.

Methods:

We searched Medline, Embase and the Cochrane Library for studies published January 2005-October 2015. We included articles written in English from high-income countries that were conducted in populations with histories of homelessness, imprisonment, sex work and substance use disorder (excluding cannabis and alcohol). Primary outcomes were measures of morbidity (prevalence or incidence) and mortality (standardised mortality rates – SMRs – and mortality rates).

Findings:

Our search identified 7946 articles, with 337 studies included. All-cause SMRs were significantly raised in 98.9% (91/92) of extracted data points and were 11.9 (95% CI 10.4–13.3; I^2 94,1%) in females and 7.9 (95% CI 7.0–8.7; I^2 99.1%) in males. Heterogeneity was high between studies. Summary SMR estimates for ICD-10 categories with two or more included data points were highest in deaths due to injury and poisoning in males (7.9; 95% CI 6.4-9.4; I^2 98.1%) and females (18.7; 95% CI 13.7-23.7; I^2 91.5%). Disease prevalence was consistently raised across infections, mental health, neoplasms, cardiovascular, gastroenterological and respiratory conditions.

Interpretation:

Socially excluded populations experience extreme health ~~inequalities~~inequities~~,~~; far greater than those observed amongst people living in areas of high social deprivation. These ~~inequalities~~ inequities occur across the full spectrum of health conditions, with the relative impact of exclusion being greater in females than males. Measures of morbidity and mortality were much higher than those observed across area based measures of social deprivation highlighting the need for better data on these populations who are largely invisible in routine health information systems. The extreme health inequity demonstrated demands intensive cross sectoral policy and service action to prevent exclusion and improve health outcomes in those already marginalised.

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Introduction

Inclusion health is a research, service, and policy agenda that aims to prevent and redress health and social inequities among people in extremes of poor health due to poverty, marginalisation and multiple morbidity (cross reference IH paper 2). ~~It is well established that in high income countries, health outcomes are strongly influenced by socioeconomic status~~The association between socioeconomic status and health outcomes is well established. For example, the standardised mortality rate~~s~~ for those aged 15–64 in the most deprived twentieth of ~~areas~~ neighbourhoods ~~of~~ in England ~~are~~ is 2.8 times the rate in the least deprived ~~areas~~ neighbourhoods for men and 2.1 times the rate for women.[1] ~~However, analyses based on geographical location may obscure~~these commonly observed social gradients in health may not capture the ~~true~~ full extent of health inequities ~~in~~ for those ~~who~~ experienc~~e~~ deep social exclusion.[1]

Previous research has described the high levels of substance use disorders (SUD) in homeless populations[2], prisoners[3], and sex workers[4], and the increased prevalence of homelessness in prisoners[5] and sex workers[6]. These marginalised populations have common intersecting characteristics and adverse life experiences that lead to deep social exclusion, making them ~~some of the most common~~powerful determinants of marginalisation in high-income settings.[7]

Marginalised populations when considered separately have been shown to have high levels of all-cause mortality.[8–10] However, despite the highly overlapping nature of the risk factors and substantially increased mortality, no previous review has attempted to examine their outcomes together.

No universally agreed theoretical framework describes inclusion health. ~~However, w~~We build on existing social exclusion theory and consider the ~~"~~'*linked and cumulative factors*'~~"~~ and processes that confound individual and group capacity for hope, opportunity, reciprocity and participation~~"~~.'.[11] Our analysis is also informed by an intersectionality perspective, which focuses on how social characteristics combine to impact on health.[2,12]

Our systematic review examines ~~the health outcomes~~mortality and morbidity in four overlapping populations ~~together~~ as exemplar determinants of deep exclusion~~:~~. ~~We aimed to systematically review and meta-analyse mortality and morbidity in~~ homeless, prison, sex work, and SUD populations ~~jointly for the first time~~.

Methods

We searched the Cochrane Library, Medline and Embase from 1 January 2005 ~~and~~ to 1 October 2015 on 27 October 2015. Full search terms are provided in the supplementary appendix. We searched for papers about the populations of interest (homeless, prison, sex workers and SUD) from systematic reviews, meta-analyses, interventional and observational studies with morbidity and mortality outcomes. We included studies identified from references of included articles.

We recognise that social exclusion has a major impact on health in other groups, such as Gypsies and Travellers and vulnerable migrants, ethic minorities, indigenous

communities and sexual and gender minorities, most notably transgender populations. Whilst these groups experience social exclusion in many high-income settings, they were considered beyond the scope of this review.

RWA screened titles, abstracts and full texts using Covidence systematic review software (https://www.covidence.org/). All authors contributed to data extraction (conducted using a Google Docs https://docs.google.com/) and data were double-checked by a second researcher (RWA, ET, GH or SVK). Extracted items included study design, year(s) of study, country, number of participants, primary outcome(s), and summary description of the study population. We attempted to contact authors if we were unable to locate papers, or required additional information about the data or study.

We attempted to identify and exclude duplicate data from research studies presented in separate publications. Where we identified multiple studies with duplicated or overlapping data (by population, time, place and outcome) we chose the study with the largest or most representative sample size, and when these were also similar, we present the most recent study. We followed the PRISMA reporting guidelines in the presentation of our manuscript. A review protocol was not published prior to conducting the review.

Outcomes

Outcomes included were measures of morbidity and mortality for ICD-10 defined conditions. Papers use a variety of measures to report outcomes. In order to ensure maximum comparability across studies for mortality outcomes, we extracted, in order of preference the first of: the first reported measure out of the following: SMRs; relative hazard ratio; mortality rate ratio; or crude mortality rate. For consistency with the majority of studies included in the review, we have not multiplied SMRs by 100. In our results a value of 1 equates to no difference between the expected and observed mortality rate. For morbidity outcomes, we extracted, in order of preference the first of: prevalence; incidence; prevalence risk ratio (PRR); incidence rate ratio (IRR); prevalence odds ratio (POR); or incidence odds ratio (IOR). Where available, we used data where the comparison group was selected as a socially deprived population or measures adjusted for area-based or income-based deprivation.

Statistical analysis

We include all extracted data in an online supplementary appendix. For the quantitative findings analysed in the paper we focus the synthesis on the primary outcome of SMRs. SMRs for all-cause mortality and by ICD-10 chapter were summarised in forest plots. We anticipated high levels of heterogeneity a-priori, and therefore created summary estimates using random effects models using Stata v.13 (Statacorp LP, College Station, TX, USA). We used the I^2 transformation to describe the proportion of total variation in study estimates due to heterogeneity.[14] We explored potential sources of heterogeneity by stratifying the analyses by country and by inclusion health population group. We describe the results of studies of disease prevalence individually. We report summary estimates of morbidity and mortality of recently published meta-analyses found by our search within our results and did not attempt to update each of these within our review. In addition to our

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Role of the funding source

The study sponsors had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. All authors had access to all the data, and were responsible for the decision to submit the manuscript.

Results

We ~~A search of the bibliographic databases was conducted on 27th October 2015 and~~ identified 7,946 articles with 1,274 duplicate articles ~~then excluded~~ (Figure 1). Of the 711 full text articles retrieved, 418 met the inclusion criteria. ~~, but a~~ We excluded a further 81 ~~were excluded~~ due to overlapping data. A total of 337 studies were included in the review, ~~with~~ including 3,219 'data points' (meaning an ~~result~~effect estimate for a unique population) ~~extracted~~ and 2,835 ~~included~~ after removal of duplicates.

The ~~included studies presented data from 38 out of 80 high-income countries (Figure 2)~~studies were from 38 countries (See Figure S1 in supplementary appendix). USA (698 data points), Australia (460), Sweden (309), Canada (257), and United Kingdom (234) ~~were the five countries with~~had the ~~highest number of~~most data~~data points (number in brackets for each) included in the review after de-duplication~~. SUD populations were the most studied sub-group ~~groups~~, accounting for ~~contributing to~~ 42.1% (1,192/2,835) of ~~all~~ data points ~~(after de-duplication)~~, followed by prisoners (27.1%; 769/2,835), homeless (26.6%; 754/2,835) and sex workers (4.2%; 119/2,835).

Infectious diseases and mental and behavioural disorders were the two most studied ICD-10 chapters with a total of 897 (31.6%; 897/2,835) and 715 (25.2%; 715/2,835) ~~included~~ data points respectively (Figure ~~3~~2). Injury and poisoning only contributed 3.4% (98/2,835) of all extracted data points. ~~Our meta-analyses focused on SMRs {(Tables 1 and 2 and Figures 3, 4, and 5)}. The most studied causes of death were 'all-cause' {(XX% of data points)} and 'injury, poisoning and external causes' {(XX% of data points)}. Most studies in the meta-analysis were of SUD groups, including {XX% (XX/XX)} studies of all-cause mortality. Cause-specific studies in males and females were split between prisoners and SUD groups, while cause-specific studies for both sexes combined were in SUD groups only. There were only {three} studies of homeless people included in the meta-analysis and none of FSW.~~
Our all-cause meta-analyses focused on SMRs, with 31 studies[10] contributing 92 data points (Table 1 & Figures 3, 4 & 5). 98.9% (91/92) of all included all-cause SMRs were increased and overall we estimated that summary all-cause SMRs were higher in females 11.9 (95% CI 10.4–13.3; I^2 94.1%) than males 7.9 (95% CI 7.0–8.7; I^2 99.1%). We provide summary estimates of SMRs, however, data were heterogeneous as measured by the I^2 statistic in many of our analyses (which we have explored further and therefore these summary measures must be interpreted with appropriate caution. Heterogeneity was not substantially reduced when

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analyses by population subgroup were undertaken. Insufficient data were available to conduct subgroup analyses by country.

Summary SMRs were higher in females than in males for ~~all-cause mortality and~~ mortality in each of the ICD-10 chapters. In some ICD-10 chapters, the summary SMR for both sexes combined did not fall between the male and female estimates. This is because the meta-analyses draw on different studies (rather than the estimate for both sexes combined being drawn from the ~~same~~male and female populations).

Infectious and parasitic diseases were the most studied disease conditions in inclusion health populations and we identified 201 papers contributing to 31.6% (897/2,835) of all data extracted (Table 2). Summary estimates of SMRs for infectious diseases were raised for males (2.8; 95% CI 1.6-4.1; I^2 65.4%) and females (5.6; 95% CI 1.5-9.7; I^2 60.0%). Disease prevalence was high but heterogeneous. HIV ranged from 0%(0/146)[15] to 61.5% (44/69)[16], Hepatitis C from 0.1% (1/734)[17] to 92.8% (64/69)[16], Hepatitis B from 1.7% (2/119)[18] to 65.0% (67/103)[19], and latent tuberculosis infection from 1.2% (1/82)[20] to 50.6% (133/263)[21].

~~It was estimated that 2.2 million prisoners globally were hepatitis C positive with the largest populations in North America (668,500).[28] A meta-analysis of the prevalence of sexually transmitted infections (STIs) in prisoners found marked wide variation and reported a pooled prevalence for Chlamydia of 5.8% (95% CI 5.0-6.5%) in men and 12.3% (95% CI 10.6-14.0%) in women; gonorrhoea, 1.4% (95% CI 1.1-1.7%) in men and 5.7% (95% CI 4.8-6.7%) in women; and syphilis, 2.5% (95% CI 2.1-2.8%) in men and 6.1% (95% CI 4.8-7.5%) in women.[29]~~

SMRs for males and females were exclusively from prison populations. SMR data for both sexes combined were from SUD populations only, with all subgroups by sex having fewer than three studies included.

Other non-communicable diseases

Summary estimates of SMRs due to neoplasms were raised in males (1.6; 95% CI 1.3-1.9; I^2 88.7%), females (1.9; 95% CI 1.3-2.5; I^2 62.8%) and both sexes combined (2.2; 95% CI 1.6-2.8; I^2 90.6%).

~~In homeless adults in Toronto, 59% had moderate, severe or very severe symptoms of dyspepsia (around twice as many as in the general population).[52] In prisoners in the USA, 4.9% of male and 9.6% of females had a history of hepatitis and 1.2% of men and 2.1% of women had a history of cirrhosis.[53] A dental survey of inmates in a juvenile detention facility in Texas showed higher Decayed, Missing or Filled scores than age and ethnicity matched population controls.[54] Dental health problems were also common in homeless people.[55]~~

The available body of evidence is largest for infectious diseases, with considerable existing research on morbidity associated with mental and behavioural disorders. In

contrast, there is a relative paucity of evidence on non-communicable diseases and injury, poisoning and external causes despite these causes having the highest SMRs across ICD-10 categories. SMRs across disease categories were consistently higher in females than males. Of the four inclusion health populations considered, sex workers were the least well investigated, which should be addressed as a matter of priority.

Our study comprehensively describes for the first time the relative mortality and morbidity burden in selected inclusion health populations. We have synthesised the significant existing literature in this area using a comprehensive search strategy to identify the current balance of evidence available to inform policymaking around inclusion health. Data were extracted and reviewed by a second author reducing the likelihood of errors. Our approach has allowed us to identify relative gaps in terms of both categories of disease and inclusion health categories. Our analysis was informed by an intersectionality perspective, which focuses on how social characteristics in combination impact on health.[7,31] We have therefore specifically investigated how the health consequences of exclusion may vary by other socially influenced characteristics, with differences by gender particularly noteworthy.

A number of limitations should be considered. Caution must be taken when interpreting the summary estimates of SMRs due to ~~the high level of~~the heterogeneity ~~found~~of studies. A lack of internationally agreed definitions ~~for the populations considered in this review means~~of inclusion health groups ~~there is variation in the levels of risk for included studies which~~ is likely to explain some of this variation. Similarly, comparison groups varied, with some studies ~~comparing to general population estimates and others to those from socially deprived areas~~using the general population and others using groups living in socially deprived areas. Studies also varied according to the extent ~~that analyses adjusted~~of adjustment for social deprivation and other risk factors. ~~However, w~~We ~~have utilised~~ used a random-effects method~~s to model the data appropriately~~ and note existing recommendations that meta-analysis should be pursued whenever possible, ~~with appropriate acknowledgement of its limitations when~~acknowledging heterogeneity ~~is high~~.[32] We limited our search to 2005 onwards and therefore ~~longer term time trends are not possible to examine with this analysis~~we have not examined longer-term trends. ~~Furthermore, there is a need for future investigation of how contextual factors, such as a country's social policies, influence health outcomes for excluded groups.~~ Lastly, for pragmatic reasons, we were unable to investigate ~~many other dimensions of social exclusion. We therefore~~other health inclusion groups and believe that further work is required to ~~investigate the health experiences of other socially excluded groups~~describe their health experiences.

We found consistently higher SMRs for females than males. Since general population mortality rates are lower in women than men for most conditions this does not necessarily indicate worse outcomes in women in inclusion health groups compared with men. ~~-~~It may ~~however~~ reflect an increased vulnerability of women in inclusion health populations or different risk distributions among women and men in inclusion health groups. SMR is a relative measure and the lower SMRs for common conditions such as cardiovascular disease and cancer may underplay the number of excess cases. Conversely, high SMRs may not indicate a large number of excess

cases if the condition is rare. Further work should report absolute as well as relative measures of mortality.

~~SMR is a relative measure, consequently less extreme SMRs seen for common conditions such as cardiovascular disease and cancer may underplay the importance of these outcomes at a population level. Conversely high SMRs for rare conditions may inflate their apparent relevance. Further work should report absolute as well as relative measures of mortality for different conditions to enable a better assessment of the contribution of different causes of mortality.~~

These extreme ~~inequalities~~ inequities demand an intensive cross-~~-~~sectoral policy and service response to prevent exclusion and improve health outcomes. An accompanying review (cross reference IH paper 2) outlines interventions that respond to these increases in morbidity and mortality. ~~Here we focus on research recommendations in relation to disease burden measurement to address issues identified by our review and we briefly discuss the health system response.~~

Determining the burden of disease remains challenging in inclusion health populations as membership of an inclusion health population is not recorded in most vital registration and health information systems. Deaths and health service usage in excluded populations are therefore a largely invisible and neglected problem as far as routine statistics are concerned. By contrast, the availability of area-based measures of social deprivation across high income countries has allowed measurement of the major population level impact of less extreme social inequalities. This has supported extensive cross sectoral policy initiatives to address these inequalities.[33] Better routine data is also needed to drive the policy response to the inclusion health agenda.

There are two broad potential approaches to tackling ~~the lack of routine mortality and health service data for inclusion health groups~~this problem. ~~Routinely recording membership of inclusion health groups in health and mortality records is a possibility~~Firstly, health services could routinely record membership of health inclusion groups. This would require ~~clear~~ agreed definitions of ~~excluded populations~~ each group~~to be agreed along with standard outcome measures~~. Those responsible for recording data would need ~~clear~~ guidance to help them ascertain membership ~~of inclusion health groups~~ and ~~sensitivity would be needed to ensure this does not reinforce~~avoid reinforcing of ~~existing~~ stigma ~~for socially excluded groups~~.[34] The feasibility of ~~routinely recording membership of these inclusion health groups~~this approach ~~-~~ outside ~~the context~~ of specialist services remains unclear. Alternatively, and more feasibly in the short term, data linkage ~~methodologies~~ methods could be used to match data from services that work with ~~excluded populations~~inclusion health groups, with vital registration data, electronic health records, and existing ~~infectious and non-communicable~~ disease surveillance systems.[35] ~~These linked datasets would then facilitate systematic estimates of mortality and morbidity over time.~~ This has been the primary method used to estimate SMRs in the studies reported in this paper. These linked datasets would facilitate systematic estimates of mortality and morbidity over time and help to measure the impact of interventions.~~Routine linkage of such datasets could facilitate systematic estimates of mortality and morbidity over time and help to measure the impact of policies and interventions.~~

As part of this wider Lancet Series we held an engagement workshop with people with lived experience of homelessness and social exclusion (described in more detail in paper 2). We asked this group about their views on collecting operational data with ethical and appropriate research governance approvals, but without specific individual level consent. Although this was only a small sample (and we acknowledge that people who face exclusion and are willing to come in to a workshop may differ from those who do not) acceptability of collection of this sort of data was extremely high. 100% of users were happy for homeless hostel records to be collected, 73% agreeing to the collection of criminal records, 62% to health records, and 85% agreeing to these records being linked together.

A vertical approach to tackling inclusion health (i.e. one that focusses on specific diseases or specific risk groups) can ~~ignore and neglect~~overlook multiple morbidity and the social issues faced by excluded populations.[36] This can result in inefficiencies and missed opportunities for prevention, early diagnosis and management as well as missed opportunities for mitigation of social risk factors. The emerging field of inclusion health should advocate for and deliver joined up health and social services for overlapping marginalised groups. These services should address not only diseases with extreme disparities, but also prevention and management of more common conditions with a lower relative risk but ~~high disease burden~~large numbers of excess cases, such as cardiovascular disease. The ability of health and social policy to address the needs of the most marginalised populations should be a key indicator of quality. Such initiatives need to be supported by ~~robust~~ information systems that can provide data for continuing advocacy, guide service development and monitor the health of marginalised populations over time.

Research in context

Evidence before this study

There is a comprehensive body of research on the health impact of ~~inequality~~inequity, much of which focusses on disparities in morbidity and mortality, and is based on ~~area based measures of social deprivation~~common measures of socioeconomic status such as neighbourhood deprivation and occupational class. The evidence of a consistent relation between ill health and increasing levels of social deprivation has underpinned a broad range of social policies and public health initiatives. Such ~~geographical based~~ analyses cannot adequately assess the extent of health ~~inequalities~~ inequity experienced by those experiencing deep social exclusion. In preparation for the inclusion health series we searched the Cochrane Library, Medline and Embase from 2000 to 30th September 2013. We searched for systematic reviews, meta-analyses, cohort and cross-sectional studies containing morbidity and mortality outcomes for the four inclusion health populations of interest (substance use disorders, homeless populations, prisoners, and sex workers). The studies identified described the highly overlapping nature of inclusion health populations, the increased risk factors for disease, and poor mortality outcomes compared with the general population.

Added value of this study

Our systematic review and meta-analysis provides the most comprehensive examination to date of morbidity and mortality outcomes across a range of inclusion health populations. We find that the extent of the health ~~inequalities~~ inequity seen in

inclusion health populations greatly exceeds that observed when comparing ~~the richest and poorest neighbourhoods~~ high and low socioeconomic groups. Extremely high mortality rates are seen across ICD-10 disease categories, with relative risks consistently higher in females than males. The relative mortality excess is greatest for injury, poisoning and external causes. However there is also high, although less extreme, relative mortality ~~inequalities~~ inequity across more common disease categories such as cardiovascular disease and cancer. Non-communicable diseases and injury, poisoning and external causes were lacking in data despite the high summary Standardised Mortality Ratio estimates. Sex workers were a particularly under-researched group.

Implications of all the available evidence

The extreme burden of disease experienced by inclusion health populations demands a cross-sectoral response to prevent deep social exclusion and an improvement in services working with these populations. This study provides the most comprehensive assessment to date of the scale and distribution of mortality in inclusion health populations in high-income countries. Our research focused on relative measures of mortality and therefore future work should examine absolute measures in greater detail. Inclusion health populations are often invisible within routine health data. This limitation can be tackled by either modifying the instruments used to collect such data or through data linkage studies. Services providing for inclusion health populations should aim to deliver health and social services for overlapping marginalised groups, in order to tackle the poor health outcomes found in this study. These services should also have a greater focus on prevention and management of more common conditions in addition to those traditionally considered high risk for inclusion health groups.

Contributors

RWA, ACH and AS proposed the hypothesis and idea for the systematic review with all authors contributing to its development and the analysis plan. RWA did the literature search. RWA reviewed studies for inclusion. RWA, SL, ET, SVK, GH performed the data extraction and checking. RWA performed all meta-analyses and wrote the first draft of the manuscript. All authors reviewed and interpreted the results and edited the manuscript.

Declaration of interests

ACH is a trustee of the Pathway: Healthcare for homeless people charity. AS is Clinical Lead and Manager for Find&Treat.

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NIHR, NHS, NHS Research Scotland, Medical Research Council, Chief Scientist's Office.

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Tables

Table 1. Characteristics of studies included in Standardised Mortality Ratio meta-analyses.

Author	Population	Population Description	Number of Participants	Country	Study Years
Nielsen[10]	Homeless	Females aged 16yr or more with at least one contact with a homeless shelter	32711	Denmark	1999-2009
Roy[37]	Homeless	Young people aged 14-25 who were "street active"	829	Canada	1995-2001
Vila-Rodriguez[38]	Homeless	A prospective community sample of adults living in single-room occupancy hotel	293	Canada	2008-2011
Graham[8]	Prisoners	Males imprisoned for the first time between 1996 and 2007	76627	United Kingdom	1996-2007
Kariminia[39]	Prisoners	All adults who had experienced full-time custody	85203	Australia	1988-2002
Pratt[40]	Prisoners	All sentenced and remanded prisoners released from prison	244988	United Kingdom	1999-2002
Arendt[41]	SUD	People receiving treatment in 'specialist institutions' for substance use disorder, reporting cocaine as their primary substance	20581	Denmark	1996-2006
Bargagli[42]	SUD	Male opiate users aged 15-69 entering treatment	2575	Netherlands	1996–2002
Barrio[43]	SUD	Regular cocaine users recruited from drug scenes and non-treatment settings	714	Spain	2004-2006
Bjornaas[44]	SUD	Individuals with opioid addiction hospitalised due to self-poisoning	185	Norway	1980-2000
Darke[45]	I	Opioid users	615	Australia	2001-2009
Degenhardt[29]	SUD	Opioid-dependent people treated with opoid substitution therapy	43789	Australia	1985–2005
Evans[46]	SUD	Young (<30yrs) injecting drug users	644	United States	2005-2007
Gibson[47]	SUD	Opioid users	2489	Australia	1980-2006
Hser[48]	SUD	Women who were admitted to drug-treatment programs	4447	United States	2000-2002
Lee[49]	SUD	Heroin users attending for opoid substitution therapy	10842	Taiwan	2006-2008
Mathers[50]	SUD	People who injected opioids and other drugs	101	Denmark	1980-1999
Merrall[50]	SUD	People in contact with drug treatment services	69456	United Kingdom	1996-2006
Nyhlen[51,52]	SUD	Substance abusers admitted for inpatient detoxification	561	Sweden	1970-2006
Pavarin[53]	SUD	Individuals who had visited a public treatment center for problems due to the use/abuse of cocaine	471	Italy	1988-2012

Rehm[54]	SUD	Participants in heroin-assisted treatment	6281	Switzerland	1994-2000
Rosca[55]	SUD	Patients who had ever been treated or were currently in treatment in methadone maintainance treatment clinics	9818	Israel	1999-2008
Singleton[56]	SUD	Drug users admitted to hospital for drug related problems	3039	Czech Republic	1997-2002
Spittal[57]	SUD	Injection drug users recruited through self-referral and street outreach	520	Canada	1996-2002
Stoove[58]	SUD	Injection drug users recruited through the social networks of 'privileged access' interviewers	220	Australia	1990-2006
van Santen[59]	SUD	Individuals from local methadone outposts, a sexually transmitted diseases clinic, and word of mouth.	1254	Netherlands	1985-2012
Zabransky[60]	SUD	Injecting drug users younger than nineteen and older than fifteen years of age.	151	Czech Republic	1996-2008
Randall[61]	SUD	All persons who came into contact with the New South Wales Opiod Substitution therapy program	43789	Australia	1985-2005
Degenhardt[62]	SUD	Canadian cohort of daily cocaine injectors	717	Canada	1996-2004
Degenhardt[63]	SUD	Opioid users	42676	Australia	1985-2006

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Table 2. Number of studies and ~~,~~ data points included in the systematic review ~~and results of meta-analysis of standardised mortality ratios~~

Commented [RA7]: To complete and double check with text

ICD-10 chapter	Number of studies	Total number of data points (% of all data points)	Number of mortality data points (% of all mortality data points)
Total	337	2835 (100)	336 (100)
All-cause	32	140 (5)	92 (27)~~31~~
Infectious and parasitic diseases	160	898 (32)	21 (6)
Neoplasms	4	145 (5)	41 (12)
Blood		18 (1)	--
Endocrine		66 (2)	6 (2)
Mental and behavioural disorders	90	715 (25)	6 (2)
Nervous system		43 (2)	6 (2)
Eye and adenexa		14 (0)	-
Ear		4 (0)	-
Diseases of the circulatory system	44	149 (5)	17 (2)
Respiratory system		79 (3)	8 (2)
Digestive system		82 (3)	34 (10)
Skin		44 (2)	-
Musculoskeletal		29 (1)	-
Injury, ~~,~~ poisoning and certain external causes		98 (3)	44 (13)
External causes		207 (7)	61 (18)
Other			

650

651 ## Figures

652

653 **Figure 1. Flowchart of included studies**

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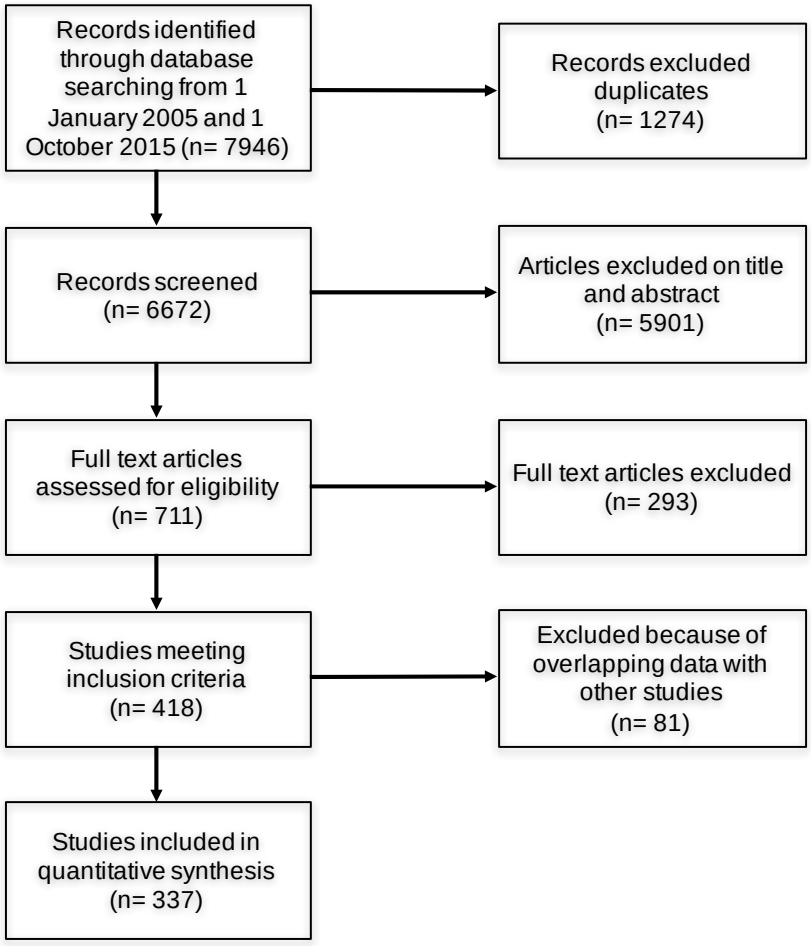

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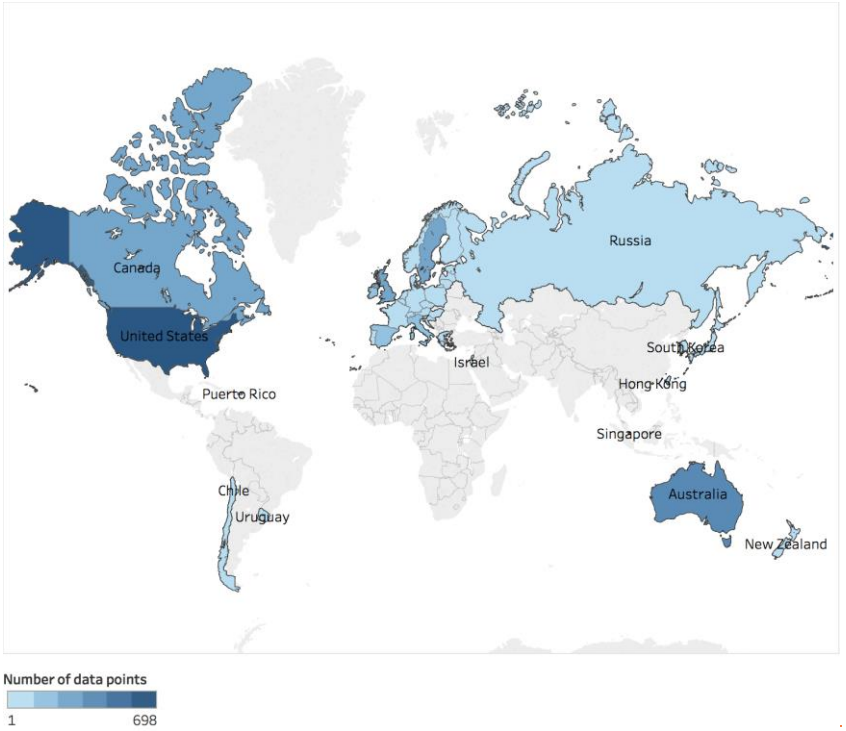
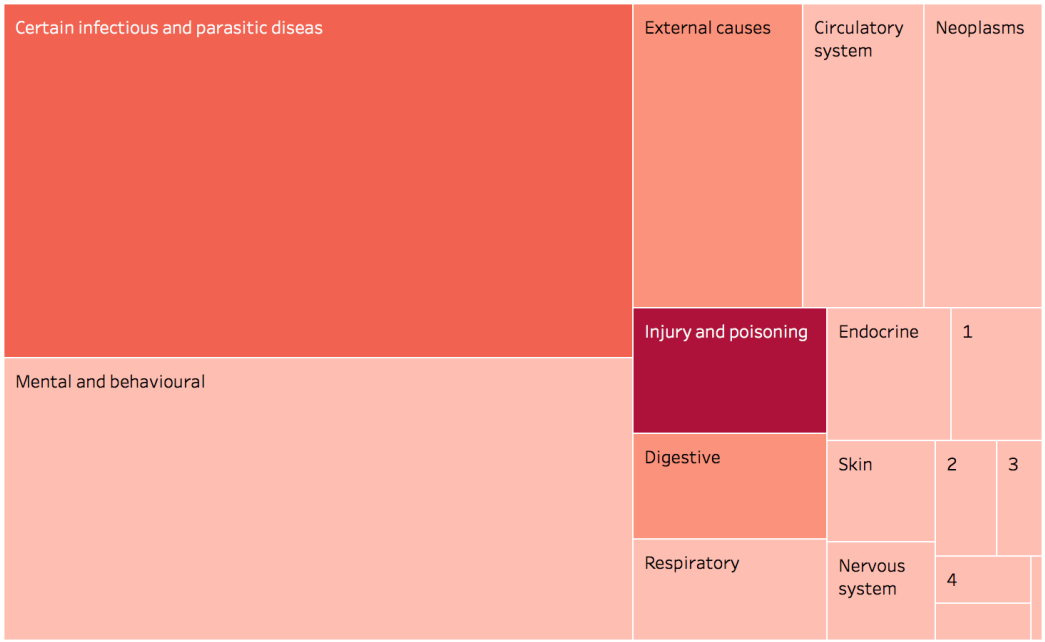
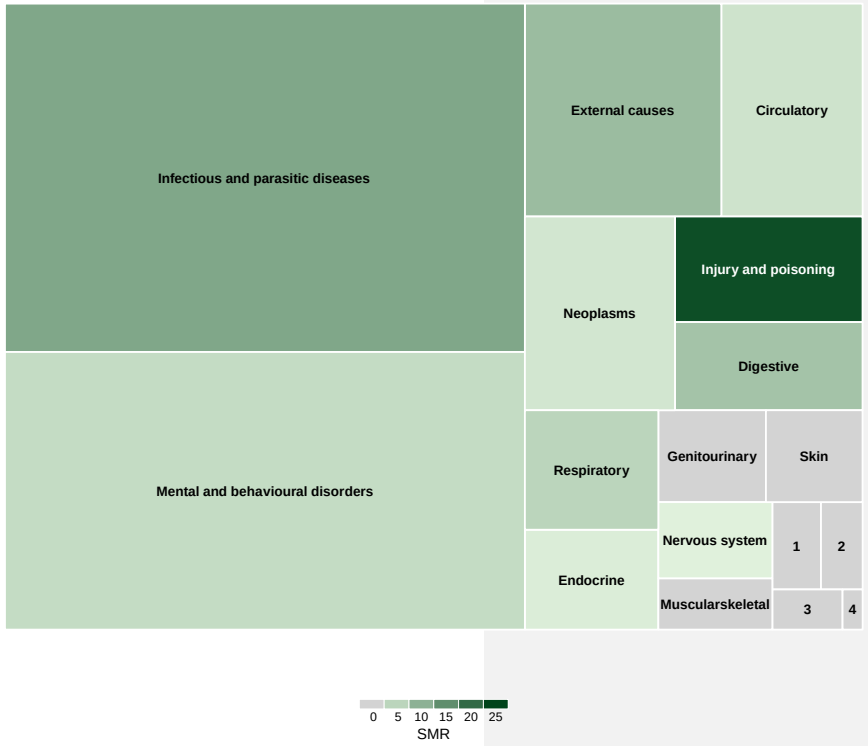
~~Figure 2. Geographical spread of existing data from high-income countries on homeless populations.~~



~~Included countries: Australia, Austria, Belgium, Canada, Chile, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Netherlands, New Zealand, Norway, Poland, Portugal, Puerto Rico, Russia, Singapore, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States, Uruguay~~

Figure ~~3~~2. Treemap summarising amount of data by ICD-10 chapter and summary estimates of SMR



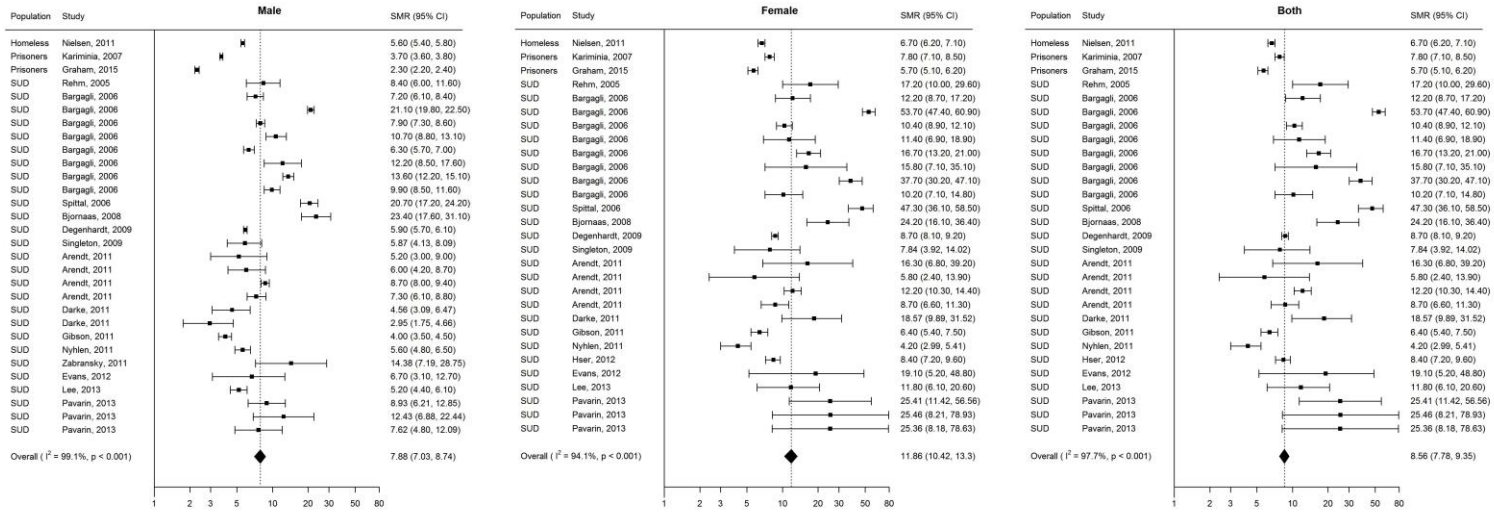


Note: Size of box indicates number of data points included (e.g. Infectious and parasitic disease = 953; Disease of Nervous system = 43). SMR used is summary estimate for ICD-10 chapter for both sexes combined. Boxes without labels are ~~1=Genitourinary; 2=Musculoskeletal;~~ 1~~3~~=symptoms, signs and abnormal clinical and laboratory findings; 4~~2~~=Ear and Mastoid process; and ~~5~~3=Eye and Adnexa; 4=. Grey boxes (with an SMR of '0') indicate that none of the studies included in this review reported SMR.

Commented [D8]: There was still one label missing. Looking at the ICD10 chapters, I'm guessing it's diseases of the blood?

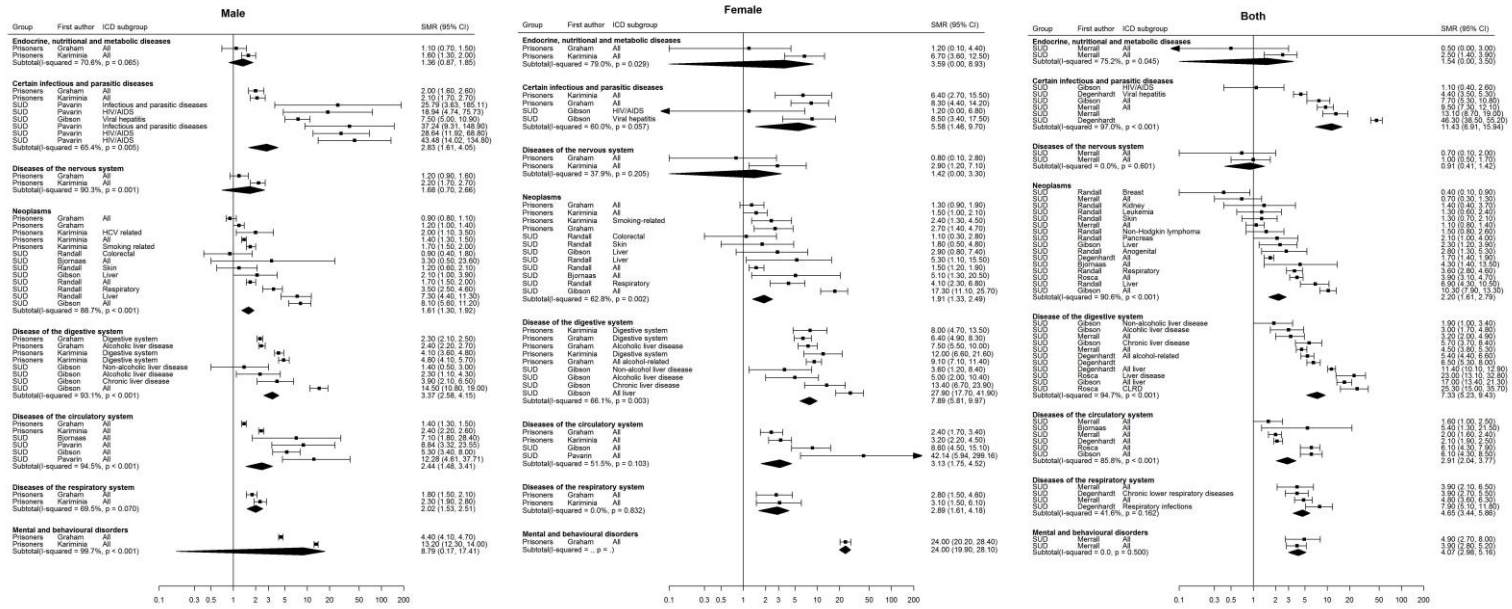
Commented [RA9]: ? Blood – to check and update before submission

Figure 43. Standardised Mortality Ratios for all-cause mortality



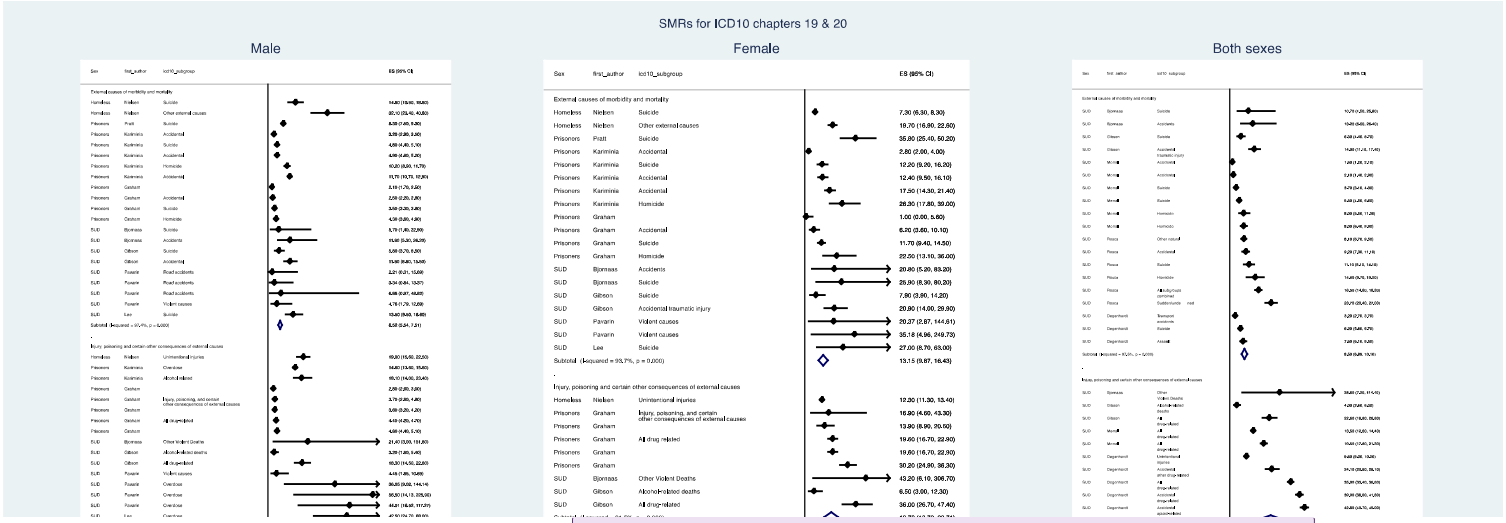
Note: Weights are from random effects analysis. Several studies contribute multiple rows of data due to different: SUD groups included (Arendt and Pavarin); countries (Bargagli); or time periods (Merrall).

Figure ~~5~~4. Standardised Mortality Ratios by ICD-10 category (excluding those due to injury and external causes).



Note: Weights are from random effects analysis. ~~SMRs greater than 60 are excluded for presentational purposes.~~ Several studies contribute multiple rows of data due to different: outcomes (Graham; Pavarin; Karimina; Randall and Gibson) and time periods included (Merrall).

Figure ~~6~~5. Standardised Mortality Ratios due to injury and external causes



Note: Weights are from random effects analysis. ~~SMRs greater than 60 are excluded for presentational purposes.~~ Several studies contribute multiple rows of data due to different: outcomes (Nielsen; Graham; Bjornaas; Gibson; Kariminia and Degenhardt) SUD ~~groups included (Pavarin); or time periods (Merrall).~~

Commented [DL10]: This might not be necessary given the log axis. Do we need to add anything in?