What is Polypharmacy In People Living With HIV/AIDS? A Systematic Review

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Abstract

Polypharmacy in people living with HIV/AIDS (PLWHA) is a rising morbidity that exacts hefty economic burden on health budgets in addition to other adverse clinical outcomes. Despite recent attempts, uncertainty remains around its exact definition in PLWHA. In this synthesis, we explored relevant databases (PUBMED, EMBASE, CROI) for studies evaluating polypharmacy in PLWHA from January 2000 to August 2021. Two independent reviewers extracted and reviewed relevant variables for analyses. The review included a total of 31 studies involving n = 53347 with a mean age of 49.5 (SD±17.0) years. There was a total of 36 definitions, with 93.5% defining polypharmacy as the concomitant use of 5 or more medications. We found significant variation in the numerical definition of polypharmacy, with studies reporting it as “minor” (N = 3); “major” (N = 29); “severe” (N = 2); “excessive” (N = 1); and “higher” (N = 1). Most studies did not incorporate a duration (84%) in their definition and excluded ART medications (67.7%). A plurality of studies in PLWHA have established that polypharmacy in this cohort of patients is the intake of ≥5 non-ART medications. To standardize the approach to addressing this rising morbidity, we recommend incorporation of this definition into national and international PLWHA treatment guidelines.

Introduction

One of the evolving challenges with regards to therapeutics in people living with HIV/AIDS (PLWHA) is the increasing number of daily medications patients often must take [1–3]. This is invariably a consequence of the rising multimorbidity associated with increasing survival seen in these patient cohorts as well as those of the general population [4]. The latter although attributable to multiple factors, the role of antiretroviral therapy (ART) drugs is by far the most important on reducing mortality of PLWHA [3]. Unfortunately, since the incorporation of these drugs into national and international treatment guidelines, the total number of HIV and non-HIV medications used by PLWHA daily has exponentially increased. This has continue to confer enormous burden on this cohort of patients [5], including the costly consequences of polypharmacy such as drug-drug [6,7], drug-food [8], and pharmacogenetic interactions [9]. In the general population, polypharmacy has often been defined as the daily ingestion of five or more medications [10]. Whilst there appears to be consensus regarding the definition of polypharmacy in the general population [10], uncertainty still exists as to what exactly constitutes polypharmacy in PLWHA [11]. This uncertainty revolves around both the numerical threshold (<5, >5, or >10 medications etc.) [11], as well as whether HIV medications [12] were part of the numerical count of polypharmacy or not. Whilst several reports have attempted to explore patterns, determinants, and consequences of polypharmacy across various populations in both inpatient and outpatient settings around the world [8,13–15], an enduring consensus around its exact definition in PLWHA remains unexplored. The most recent attempt at a numerical characterization of polypharmacy in this cohort of patients was a narrative review by Back et al [1]. A recent meta-analysis by Danjuma et al explored for the first time the prevalence as well as global trends of polypharmacy across different demographic populations of PLWHA. It reported a period prevalent rate of polypharmacy amongst PLWHA of around 33% across the world and rising. Notably

most of the studies included in this review synthesis had different medication thresholds for what constitutes polypharmacy. In this study, we aimed to carry out a comprehensive synthesis of all studies that have investigated polypharmacy in PLWHA with the view to ascertaining what exactly constitutes polypharmacy in this cohort of patients; and in so doing engender potentially useful prescriptive consensus around this rising morbidity.

Method

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist and the Cochrane Handbook guidelines [16]. The protocol was registered on the International Prospective Register of Systematic Reviews **(PROSPERO)— CRD42020170071**.

Data sources and searches

The following databases were searched from 1st January 2000 to 30th August 2021: PubMed; EMBASE, Conference on Retroviruses and Opportunistic Infections (CROI), Cochrane Database of Systematic Reviews; Science Citation Index and Database of Abstracts of Reviews of Effects (DARE). Reference lists of included studies were also manually searched to identify relevant articles that were not yielded from the database search. Databases were searched using the Boolean operator 'AND' to combine terms from different categories, while 'OR' was utilized for terms under one category. The following Medical Subject Headings (MeSH) terms and keywords were used: (HIV [tiab] OR "people living with HIV" [MeSH] AND polypharmacy[tiab]).

Eligibility criteria

Studies were considered for inclusion if they were published in English language between 1st January 2000 and 30th august 2021; and focused on PLWHA with age greater than 18 years old. All studies that incorporated at least one definition (numerical, descriptive or both) of polypharmacy amongst PLWHA on ART medicines were eligible for inclusion irrespective of design. We excluded studies that failed to clearly define what constitutes polypharmacy either numerically or descriptively in their methodology.

Study selection

Following completion of literature search from relevant databases, duplicates were removed utilizing EndNote 20® (2021 Clarivate). Screening of titles, abstracts (using Rayyan QCRI software), and full papers (using Microsoft excel) was conducted independently by two reviewers (SK and FA) according to the inclusion and exclusion criteria. Discrepancies were resolved through consensus or by adjudication by a third reviewer (MID).

Data extraction

A data extraction form was designed by two reviewers (MID and SK) and piloted on 5 included studies. We extracted the following variables from each study: first author, year of publication, center where the

study was carried out, number of PLWHA, polypharmacy definition, number of patients satisfying criteria for polypharmacy, socio-demographic parameters. Where studies explored different definitions of polypharmacy, we included all definitions under respective category. Statistical analyses were conducted in Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC. 2021.

Results

Figure 1 gives a PRISMA chart of result of our search strategy and studies included in this synthesis. We identified a total of *N* = 31 studies [2,6,8,11–13,15,17–40] across 4 continents (Figure 2) that fulfilled the criteria for inclusion in the systematic review.

The total number of patients with polypharmacy as defined by the included studies was (N = 53347). The mean age of the patient cohort was 49.5 (SD±17.0) years, a significant proportion of which were males (67%). There was a total of 36 definitions of polypharmacy, with studies further divided based on the magnitude of polypharmacy (Table 1); minor polypharmacy (N = 3); major polypharmacy (N = 29); “severe” polypharmacy (N = 2); “excessive” polypharmacy (N = 1); “higher” polypharmacy (N = 1) (Table 2).

Table 1. Broad classification of Polypharmacy by the reviewed studies

Term	Number of Drugs	Number of studies *N*	Reference
Polypharmacy			
Minor	>2	1	[12]
	>3	1	[12]
	>4	1	[13]
Major Polypharmacy	>5	29	[2], [6],[8],[15],[17-29],[31-40]
	>6	2	[11][25]
	>10	3	[23] [26] [39]
	>11	1	[11][25]
	>21	1	[11]

Table 2. Descriptive terms used by included studies to define polypharmacy

Polypharmacy	Frequency (*N*)	Reference
Minor	3	[12][13]
Major	29	[2], [6],[8],[15],[17-29],[31-40]
Severe	2	[23] [26] [39]
Excessive	1	[11]
Higher	1	[39]

Duration of Polypharmacy

Amongst the included studies, 16% (N = 5) incorporated the duration of treatment to the definition of polypharmacy, while a significant proportion 84% (N = 26) only provided the numerical definition of polypharmacy with no additional information on its duration. Gimeno-Gracia et al. further stratified drug exposure based on the following duration: greater than 1 day; greater than 90 days; and greater than 180 days [14,36]. Three studies included a duration of more than or equal to 4 consecutive months [17, 20, 30]. In their definition of polypharmacy, Justice et al. included the duration of more than or equal to 90 consecutive days [12].

Numerical definition of polypharmacy in PLWHA

There was marked variation in the numerical definition of polypharmacy, with studies reporting it as “minor”, “major”, “excessive”, “severe”, and “higher”. Of the studies included in our review, 93.5% (N = 29) defined polypharmacy as the concomitant use of greater than or equal to 5 medications. Several studies had “outlying” definitions for polypharmacy that were different from those mentioned in other studies. These definitions included >2 [12]; > 3[12]; > 4 [13] ; >6 [25][11]; >10 [39][39][26]; >11 [11][25]; > 21 [11].

ART or non-ART medication polypharmacy

With regards to constituents of medication regimen included in the definitions, 67.7% of studies (N = 21) specified that the polypharmacy definition included only non-ART medications, while 27% (N = 9) studies included both ART and non-ART medications in their definitions. One study did not specify whether ART and non-ART medications were used as part of the adjudication process of polypharmacy (3.2%) [23].

Discussion

To our knowledge, this review represents the first comprehensive systematic synthesis of studies that have explored polypharmacy in PLWHA to define what the term polypharmacy entails in this context. We have identified and evaluated 31 studies that defined polypharmacy in PLWHA forming a pooled sample size of 53347 from eleven countries. We found wide variability in the way polypharmacy is defined amongst PLWHA with an iteration of a total of 36 definitions from the reviewed studies. We found a

significant proportion (93.5%) of studies included in our report defined polypharmacy as ≥5 concomitant medications. Additionally, up to 67.7% have explicitly specified these concomitant medications as non-ART medications. Following a systematic synthesis of the results from all studies, we found that a definition of polypharmacy including ≥5 non-ART medications over any period is representative of what the majority of studies put forth as their definition.

Several recent studies have identified HIV polypharmacy as a growing problem that needs to be addressed. However, the lack of consensus around a unified definition hindered attempts at exactly estimating the burden as well as robust appraisal of its consequences and interventions to mitigate its effect on therapeutics. Without adequately defining what constitutes polypharmacy, researchers, administrators, and clinicians are all liable to grossly misidentifying patients who are at risk for polypharmacy. This leaves patients susceptible to the dangerous (but avoidable) harms associated with polypharmacy including problematic interactions (drug-drug, drug-food, and pharmacogenetic), adverse effects, rising therapeutic costs, medication non-concordance, increased hospitalizations, and sometimes avoidable mortality [2]. The situation is especially dire in PLWHA since they are a high-risk population ab initio with a high pill burden due to their rigid ART medication regimes. What has exacerbated this in recent years amongst these patient cohorts, is their increasing survival often associated with a tandem rise in prevalence of associated comorbidities [12,21,36,41,42]. Taken together, this provides the enabling milieu for potentially harmful polypharmacy to ensue often with far reaching implication for a range of morbidities as highlighted above.

Having a unified definition for polypharmacy ensures that at hospital, community, and administrative levels therapeutic decisions regarding the pill burden of PLWHA are more nuanced and uniform. Additionally, a well-established definition can also assists strengthening and clarifying communication between different stakeholders to for example help encourage mindfulness and attention while prescribing medications and minimize downstream adverse outcomes in these cohorts of patients. Finally, having a standardized definition for polypharmacy will allow a more robust comparison of parameters and outcomes related to pill burden in PLWHA and hence draw more precise conclusions.

Although most studies (93.5%) defined polypharmacy as the use of 5 or more medications, there were several “outlier” studies that explored alternative definitions. The “outlier” definitions ranged from as low as ‘>2 medications’ to as high as ‘>21 medications’, and it wasn’t immediately apparent from reviewing these studies how these thresholds were arrived at. From the average pill count of PLWHA starting at 3 medications, it is unlikely that adoption of polypharmacy thresholds <5 in these patients is likely to be of any determinative value as literally all population of PLWHA will thus be classified as “cases”. Conversely, definitions at the upper part of the extreme (such as >21 medications) are likely misclassify a significant proportion of PLWHA with high pill burden but which has not reached the high threshold of 21 medications. Yet other studies employed descriptive terms such as “excessive” [11] or “severe” (>10 Medications) [23][26], and “higher” [39] polypharmacy to convey the magnitude of pill burden, but these subcategories were not consistently mentioned across all studies.

Although, incorporating duration of drug exposure into the definition of polypharmacy allows for a better understanding of the magnitude of the problem, the time threshold it prescribes has the potential to preclude some patient cohorts from beneficial interventions simply because they fail to satisfy this arbitrary exposure thresholds. In our review, two studies included the duration of at least 4 months in their definition of polypharmacy (Nozza et al., Guaraldi et al.)[20][17] while most other studies did not specify a duration. A patient taking several medications for 3 months may not be classified as a polypharmacy case according to these two studies but may be considered a polypharmacy case according to studies that did not include a duration of drug exposure in their definition. This has serious implications when it comes to deciding which patients will benefit from interventions aimed at reducing the harms caused by polypharmacy. If one definition of polypharmacy required a duration of more than 4 months, patient A who took 6 medications for 5 months would be offered interventions while patient B who took 9 medications for 2 months would not be a candidate for the same interventions although both patients may be exposed to the same adverse outcomes of polypharmacy; including drug-drug, drug-food, and pharmacogenetic interactions amongst others. If a patient met the numerical criteria of polypharmacy but did not meet the criteria in terms of duration, they should not be excluded from interventions that address the effects of polypharmacy. The decision about whether a patient will benefit from interventions should be solely based on the adverse effects they are experiencing secondary to polypharmacy.

When incorporating duration as part of the polypharmacy definition, and when this same definition is used as criteria to guide interventions, it is important to consider both the number of medications and the duration of use simultaneously. If a patient has been using medications for a long time, fewer number of medications should be acceptable to meet the criteria for polypharmacy. Alternatively, if a patient has been using an excessively large number of medications but for a short period of time, interpretation of the duration of medication exposure should be more nuanced. In the general population for instance, before Masnoon et al's consensus review [10], Nishtala et al [43] defined polypharmacy as the use of five to nine medications for 90 days or more, while Veehof et al. [44] described it as the ingestion of two or more medications for more than 240 days in a year. Although the duration was longer in the definition proposed by Veehof et al., the threshold for number of medications was lower in Nishtala et al.

Studies may agree with regards to the duration of medication exposure, but still diverge with regards to the numerical definition of polypharmacy. In patients with PLWHA, it is our observation that consistency amongst studies in only one component of polypharmacy definition (e.g. duration) is not enough. For instance, Nozza et al. [20], Guaraldi et al. [17], and Alleman et al. [30] all included a duration of 4 months in their definitions, different medication thresholds for what constitutes polypharmacy. More specifically, Alleman et al. considers more than 3 medications as polypharmacy while Nozza et al., and Guaraldi et al. consider more than 5 medications. According to the polypharmacy definition proposed by Alleman et al., a patient taking 4 medications for a duration of 5 months would fall under the definition of polypharmacy and may be eligible for interventions, but the same patient may not be offered interventions according to Nozza et al. or Guaraldi et al. This highlights the importance of having consistency in terms of both number of medications as well as duration of treatment.

While the majority (67.7%) of studies included in our review only comprised non-ART medications in their definitions of polypharmacy, a significant proportion (27%) embraced both ART and non-ART medications. Kara et al. [18] included both categories in their definition of polypharmacy, while Halloran et al. [6] only involved non-ART; although both studies had the same numerical definition for polypharmacy (5 or more medications). A patient taking three ART and three non-ART medications will meet the criteria for polypharmacy according to Kara et al. but not Halloran et al. Consistency with regards to the classes of medications included in the definition of polypharmacy is essential. The standard HIV regimen consists of at least 3 ART medications [45]. Therefore, with regards to PLWHA, we recommend that only non-ART medications be included in the definition of polypharmacy as all PLWHA will be on at least 3 ART medications.

Strengths & Limitations:

The key strength of this study lies in its novelty as the first attempt at unifying the various interactions of polypharmacy definitions in PLWHA currently in use in existing literature; thus providing therapeutic policy makers, researchers, and clinicians with an important tool to classify PLWHA in the context of polypharmacy. Furthermore, our methodology anchored on a robust systematic synthesis of current evidence from a plurality of studies contrast significantly from previous attempts that expounded a narrative inference to resolving this uncertainty. Finally, due to its loose inclusion criteria (both observational cohort studies and randomized controlled trials) that have allowed us to analyze a large pooled sample size. This lends external validity to the study and ensures that the results are generalizable to greater and more diverse populations.

As has been observed from previous exploration of these data schemes, our study was limited by the same constraints; including missing data that sometimes could not be retrieved from some of the authors of the included studies; large variability and imprecise data points that may skew our results. Additionally, we have only included studies that were published in English language, it is however unlikely that the range of uncaptured data from studies in other languages are likely to alter the final point estimate of polypharmacy definition in any meaningful way. Despite this, the findings of this review are likely to engender a more robust and reproducible consensus around this rising morbidity.

Conclusion

A plurality of studies in PLWHA have established that polypharmacy in this cohort of patients is the intake of ≥5 non-ART medications. We recommend the incorporation of this definition into national and international PLWHA treatment guidelines in order to standardize the approach to addressing this rising morbidity.

Declarations

Data availability

All data relating to this work is available from the corresponding author on reasonable request.

Conflict of interest

None of the authors have any conflict of interest to declare

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Author contribution

MID was involved in review concept development, regulatory/PROSPERO approval, independent reviews, and data analyses, writing initial and final manuscript draft; SK and FW were involved in independent reviews and data collection; LMN was involved in collecting and analyzing data; all authors (MID, SK, FW, LMN, AE) were involved in writing and reviewing the manuscript.

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Figures

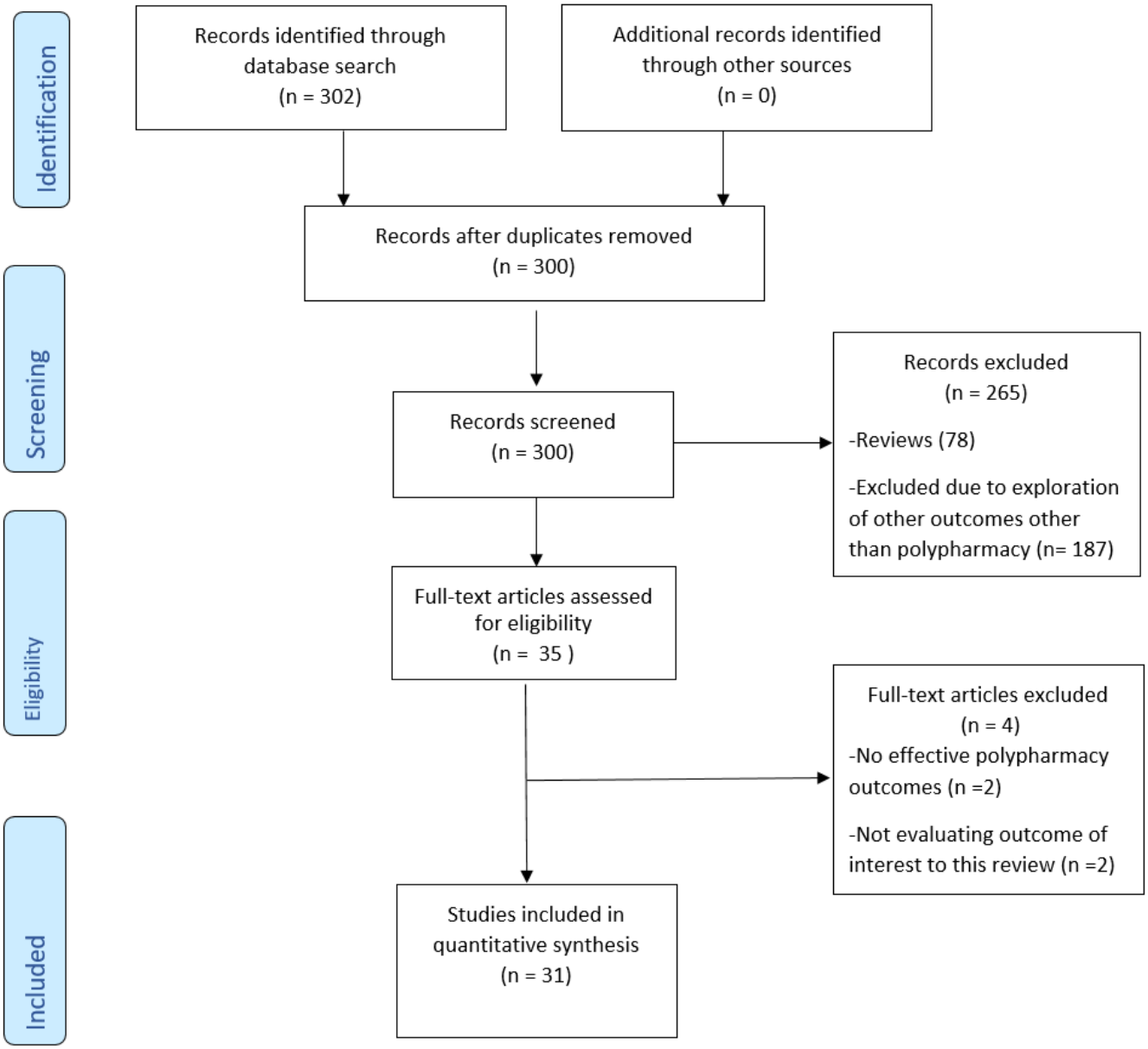

Figure 1

PRISMA Flow chart for study selection

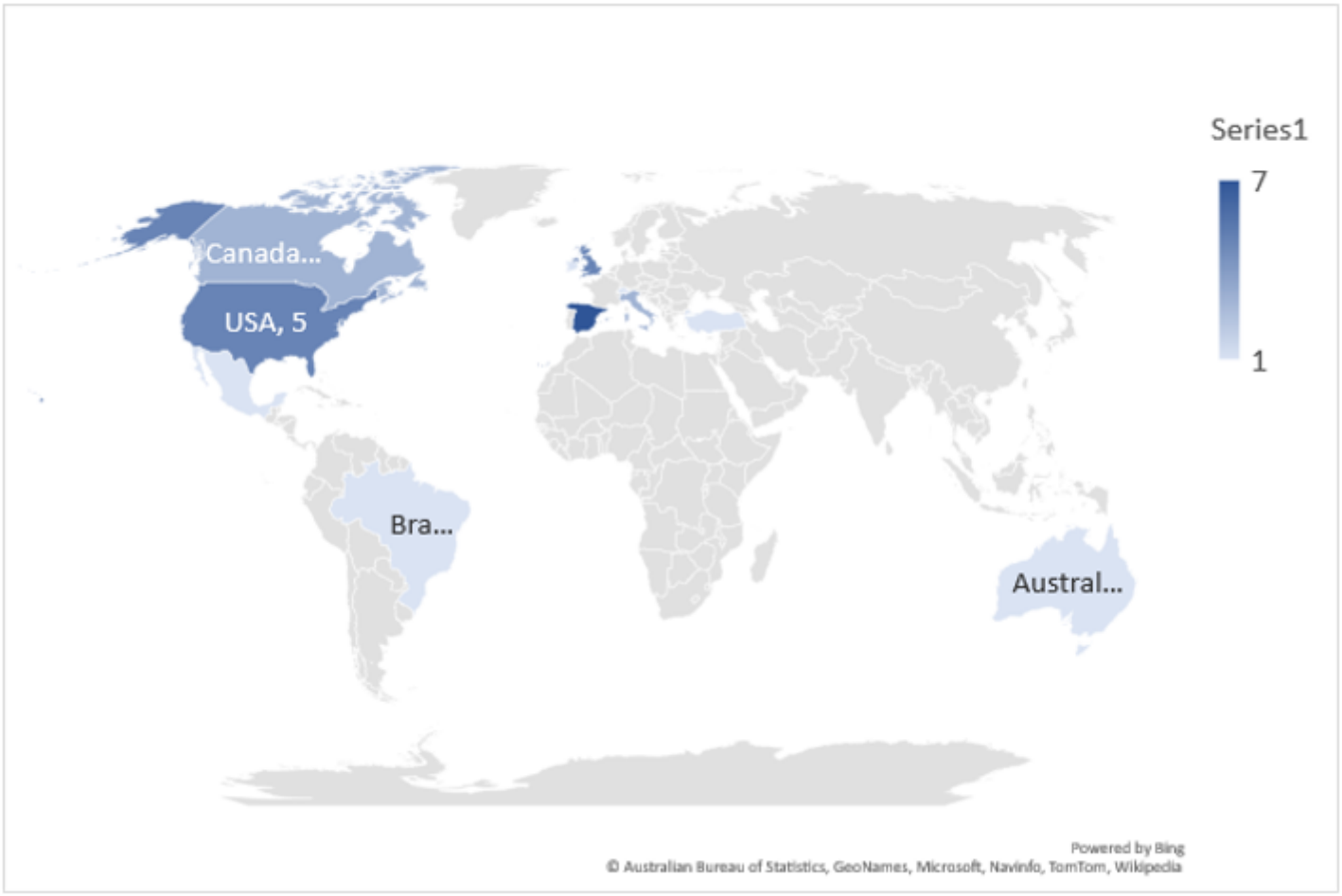

Figure 2

Map showing the distribution of studies included in the review