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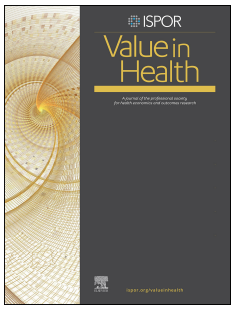

"What's sex and gender got to do with it?" A scoping review of sex and gender-based analysis in pharmacoepidemiologic studies of medication adherence

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ABSTRACT

Background: Medication taking is a complex multidimensional behaviour that may be impeded by a range of biological and psychosocial factors, including sex and gender. We aimed to synthesize how sex and gender have been reported and analyzed in pharmacoepidemiologic studies of medication.

Methods: We searched for English-language peer-reviewed articles of observational studies (e.g., cross-sectional, cohort, case-control) that examined medication adherence among adults and included sex and/or gender in their reporting.

Results: We included 937 studies among 530,537,287 participants published between 1979 and 2021. Most studies were cross-sectional (47%), lasted $\leq$ 1 year (35%), examined self-reported adherence (53%), did not assess specific adherence problem(s) (40%), and included medications for cardiovascular conditions (24%) or systemic infections (24%). A quarter (25%) of studies used sex and gender interchangeably, over a third (36%) of studies that reported gender data likely collected data on sex, and less than 1% of studies described sex and gender as distinct variables. Studies of cisgender participants more often reported that females/women experienced greater adherence problems compared to often than males/men (31% vs 20%), particularly discontinuation and cost-related non-adherence. Only 21 studies (2%) reported on transgender individuals, and these predominantly examined antiretroviral medications for HIV.

Conclusions: Our review revealed substantial conflation of sex and gender in studies of medication adherence as well as a paucity of research among transgender individuals. Moreover, our synthesis showed sex/gender disparities in medication taking with studies reporting greater medication adherence problems among cisgender women and transgender participants compared to cisgender men.

Key words: sex and gender-based analysis, medication adherence, pharmacoepidemiology, observational studies, scoping review

HIGHLIGHTS

- Medication taking, a widely studied problem within the field of pharmacoepidemiology, is a complex multidimensional behaviour that may be impeded by a range of biological and psychosocial factors, including sex and gender.
- Our review revealed inconsistent and insufficient sex and gender considerations among studies of medication adherence, a paucity of studies among transgender individuals, and substantial sex/gender disparities in medication adherence.
- Our findings support growing calls to improve the examination of sex and gender in health research and highlight the need to explore new methodologies for appraising the diverse, nuanced, and intersectional dimensions of gender within pharmacoepidemiologic research.

BACKGROUND

Prescription medications are necessary for disease prevention and management, particularly for people living with chronic conditions. Both sex and gender have been recognized to influence health and health behaviours, such as medication adherence; however, these complex biological and psychosocial constructs are often inadequately and inappropriately addressed in health research.

While sex and gender are related concepts, they are not equivalent. Sex refers to a set of biological attributes and is associated with anatomical, physiological, genetic, and hormonal features(1, 2). Health research often oversimplifies sex as a binary variable (female and male) based on external reproductive anatomy and functions, disregarding that sex differentiation is governed by at least 12 genes besides those of the X and Y chromosomes, sex exists across a continuum of possible sex-based characteristics, and up to 2% of people are intersex(1, 3, 4). Gender refers to socially constructed roles, behaviours, and expressions; nonetheless, it is often conceptualized as binary (girl/woman and boy/man) and confused with sex in health research(1). In reality, gender is complex, shifting, and encompasses a spectrum of identities including those used by individuals who do not identify as solely feminine or masculine (e.g., agender, genderfluid, gender queer, and non-binary are some contemporary examples; although this language is continually evolving)(5). While the conceptualization of gender may begin with sex, gender is a multidimensional social construct influenced by how people experience their physical bodies, how people perceive themselves (gender identity), how people present their gender in society (gender expression), how others interact with them (social gender), and the distribution of power and resources in society(1, 2). Furthermore, people may not feel their sex and gender are congruent. Transgender is used to

describe people whose gender identity does not align with their birth-assigned sex, while cisgender describes people whose gender identity aligns with their birth-assigned sex(6).

Medication taking is a complex multidimensional behaviour that may be impeded by a range of biological and psychosocial factors. Biologically, females have been shown to have a 1.5 to 1.7 fold greater risk of experiencing adverse drug reactions as a result of sex differences in pharmacokinetics (i.e., drug absorption, distribution, metabolism, and excretion over time) and pharmacodynamics (i.e., intensity of therapeutic and adverse effects over time)(7-9). Moreover, numerous individual and systemic reasons have been shown to affect medication adherence. Specifically, factors related to the patient (e.g., decreased age, low health literacy, religious/cultural beliefs, lack of social support from family and friends), their health (e.g., physical/cognitive impairments, alcohol/substance use), their medication treatment (e.g., negative beliefs about medications, complex regimens), and the financial and healthcare system (e.g., poor patient-provider relationship, lack of permanent housing, lack of insurance coverage) are associated with poorer adherence(10). Studies specifically examining the effect of gender on medication adherence have shown variable and inconsistent findings(10).

Following growing calls for health research to meaningfully and appropriately incorporate sex and gender(2, 11, 12), several reviews published in recent years have evaluated the analysis and reporting of sex and gender across a range of research fields(13-22). To our knowledge, this has not been done within the field of pharmacoepidemiology nor, specifically, medication adherence. Through conducting a scoping review of the published literature, we aimed to synthesize how sex and gender have been analysed and reported in medication adherence research and what is known of the relationship between sex and/or gender and adherence to prescription medications.

METHODS

Search strategy and study selection

Following methodological guidelines for scoping reviews by the Joanna Briggs Institute(23), we developed our search strategy parameters with a health science librarian who executed the search. We searched Ovid MEDLINE, Ovid Embase, and CINAHL from inception to February 3, 2021, using subject headings and keywords related to medication adherence, sex, gender, and observational study designs (see Supplementary materials Table S1). Our inclusion criteria included peer-reviewed manuscripts that: 1) used a sample of adult patients (≥ 18 years) taking prescription medication(s); 2) employed an observational study design (e.g., cross-sectional, cohort, case-control); 3) used quantitative data sources (e.g., administrative health data, medical records, surveys, etc.); 4) assessed medication adherence; 5) included a sex and/or gender variable; and 6) were published in English. We excluded studies that examined mass drug administration programs, vaccinations, or restarting medications following discontinuation. Records were exported into Covidence where duplicates were removed. Two reviewers first screened the titles and abstracts to determine their eligibility and, subsequently, one reviewer reviewed the full texts of eligible citations. Citations meeting the inclusion criteria were forwarded to data extraction.

Data extraction

We developed a data extraction form in Excel to collect necessary information for data synthesis. Information on study characteristics included publication year, country, study period, study design, data sources, number of analytic samples, and sample size. Information on adherence included studied medication(s) categorised by their Anatomical Therapeutic Chemical (ATC) group, types of medication taking problem(s) examined (i.e., cost-related non-adherence, non-initiation, poor implementation, discontinuation, or non-specific non-adherence), and source of adherence

measurement (e.g., self-reported, medical records or insurance claims, electronic monitoring, pill count, blood serum/urine metabolites). A key issue in medication adherence research is the lack of uniformity in the terminology and methods used to assess medication taking behaviours(24). As such, we grouped the types of medication problem(s) based on quantifiable definitions proposed by the European Society for Patient Adherence, Compliance, and Persistence(24) (i.e.., non-initiation, poor implementation, and discontinuation) and other types of non-adherence pervasive in the current literature (i.e., cost-related non-adherence), where 'non-specific non-adherence' included studies that did not clearly examine a specific or quantifiable adherence problem. Of particular interest was information on the distribution of sex/gender groups in the study sample, reported sex/gender variable(s) (e.g., sex, gender, both, neither) and sex/gender groups (e.g., male, female, man, woman, cisgender, transgender), method(s) of examining sex/gender (e.g., sample distribution by sex/gender, descriptive statistics of sample characteristics by sex/gender, descriptive statistics of adherence by sex/gender, bivariate analysis of adherence and sex/gender, multivariable analysis of adherence with a sex/gender covariate, multivariable analysis of adherence stratified by sex/gender, cohort matching by sex/gender), and descriptive results of sex/gender analysis of adherence (i.e., results showing statistically significant differences between two or more sex/gender groups assessed through bivariate or multivariate analysis). One reviewer preformed data extraction and synthesized the results. Descriptive statistics were conducted using SAS Studio 3.8 (SAS Institute, Cary, North Carolina).

In the subsequent section, we have reported on the language used to describe sex and gender variables and groups among included publications. It important to note that we were not able to assess whether this language was used accurately or appropriately since we did not have access to the authors' data collection tools. As included studies used a range of different descriptors of sex

and gender variables and groups in addition to some using these terms interchangeably, we have used "/" when the studies we are summarizing used more than one variable (e.g., sex/gender) or group (e.g., females/women) descriptor.

RESULTS

Included studies

Our search identified 8,904 unique citations after removing duplicates. Following screening, 937 studies were included in the review (see Supplementary materials Figure S1). The characteristics of the included studies are summarized in Table 1. Most studies employed a cross-sectional design (47%), had a duration of less than 1 year (35%), assessed adherence through self-reported measures (53%), did not assess a specific problem of adherence (i.e., non-initiation, poor implementation, discontinuation, or cost-related non-adherence; 40%), and were conducted within the continental regions of North America (33%), Asia (26%), and Europe (26%). The year of publication and country of included studies are shown in Supplementary materials Figure S2. Adherence to medications with indications for the cardiovascular system (e.g., hypertension, hyperlipidemia; 24%), systemic infections (e.g., HIV, tuberculosis; 24%), the alimentary tract and metabolism (e.g., diabetes, inflammatory bowel disease; 15%), antineoplastic and immunomodulating agents (e.g., biologics, chemotherapy agents; 13%), and the nervous system (e.g., depression, bipolar disorder, schizophrenia; 11%) was most often assessed.

Description of study samples

While most studies (919; 92%) had a single study sample, there were 18 studies that reported on more than one study sample (85 additional samples) with distinctions between samples related to differences in medication(s), disease, data source(s), country, and age group. In total, we

summarized findings from 1,004 study samples, with a median size of 525 participants (interquartile range [IQR]: 204 – 4647; min: 10, max: 23,832,952).

With respect to reported sex/gender groups, 41 study samples included a single group, 949 included 2 groups, and 14 included 3 or more groups. Study samples with one sex/gender group (n=41) predominantly included males/cisgender men (28; 68%), followed by females/cisgender women (11; 27%), and transgender women (2; 5%). Study samples with two sex/gender groups (n=949) predominantly involved cisgender participants (942; 99%) with a median 52% distribution of females/women (IQR: 42 – 61; min: 2, max: 98) and 48% distribution of males/men (IQR: 39 – 58; min: 2, max: 98). Two samples with cisgender participants neglected to label the sex/gender of included groups. Additionally, 4 study samples (<1%) included males/cisgender men and transgender women, and 1 study sample (<1%) included cisgender men and transgender participants without specifying their sex or gender. Of the samples with three or more sex/gender groups (n=14), half (7; 50%) included males/men, females/women, and transgender participants without specifying their sex or gender. Additionally, 5 (36%) study samples included both cisgender and transgender males/men and females/women and 2 (14%) study samples included males/cisgender men, females/cisgender women, and transgender women. Overall, transgender participants accounted for a median 5% (IQR: 1 – 12; min: 1, max: 100) of the 21 studies that included them.

Sex/gender reporting among included studies

The sex and gender variables researchers reported using varied across studies. Overall, 379 (41%) studies used gender, 283 (30%) used sex, 246 (26%) used sex and gender interchangeably, 23 (2%) didn't specify whether they used sex or gender (i.e., this included predominately single sex/gender

group studies), and 6 (1%) used both sex and gender as distinct variables (Figure 1a). It's unclear whether included studies accurately described the sex/gender variables available to them. For example, of the studies that reported using gender, 137 (36%) used data sources (e.g., medical records, insurance claims, etc.) that likely only collected data on participants' birth-assigned sex. Figure 1b shows reported sex/gender variable(s) stratified by ATC group. Excluding studies examining adherence to ATC H (systemic hormonal preparations) and P drugs (antiparasitic products, insecticides, and repellents) which did not use gender in their reporting, studies using gender only ranged from 25% to 57% among those examining ATC D (dermatologicals) and ATC V (various) drugs, respectively. Excluding studies examining adherence to ATC V drugs which did not use sex in their reporting, studies using sex only ranged from 16% to 57% among those examining ATC G (genitourinary system and sex hormones) and ATC P drugs, respectively. Studies using sex and gender interchangeably ranged from 18% to 71% among those examining ATC L (antineoplastic and immunomodulating agents) and ATC H drugs, respectively. All studies that used both sex and gender as distinct variables in their reporting examined ATC J drugs. Of the studies that reported on gender, the proportion of studies that likely only collected data on participants' birth-assigned sex ranged from 14% to 75% among those that did not specify the drugs they examined and those examining ATC V drugs, respectively.

The language studies used to describe distinct sex and gender groups varied considerably irrespective of the specified sex/gender variable reported (Figure 1c). Most studies (55-64%) used males/females and men/women interchangeably to describe cisgender participants. When distinctions were made, studies that used sex only, gender only, or used them interchangeably (n=908) used males/females (32-41%) more often than men/women (4-6%) whereas studies that

did not specify whether they used sex or gender (n=23) used men/women (30%) more often than males/females (9%).

Table 2a shows the reporting of sex/gender variables and the language used to describe participants' sex/gender among the 21 studies that included transgender individuals. All studies that used both sex and gender as distinct variables included transgender participants. In total, 8 (38%) studies reported including transgender participants without specifying their sex or gender. Only 5 of 19 (26%) studies that included cisgender and transgender participants used 'cisgender' at any point in their reporting when referring to cisgender participants. Among studies that included transgender participants, all except one study investigated adherence to antiretroviral medications for the prevention and treatment of HIV.

Sex/gender-based analysis

Methods of incorporating sex/gender-based analysis varied across studies. Overall, 931 (99%) reported the distribution of sex/gender groups within all included study samples, 93 (10%) reported descriptive statistics of sample characteristics by sex/gender, 465 (50%) reported descriptive statistics of adherence by sex/gender, 575 (61%) reported results of bivariate analysis of adherence and sex/gender, 548 (58%) reported results of multivariable analysis of adherence and a sex/gender covariate, 40 (4%) reported results of multivariable analysis of adherence stratified by sex/gender, and 17 (2%) matched participants' sex/gender.

The type of adherence problems assessed by study sample and proportion of samples that reported results of conducted bivariate and multivariable sex/gender-based analysis of adherence are shown in Figure 2a. Results among cisgender participants are summarized by type of adherence problem

and non-adherence overall in Figure 2b. Overall, 49% did not show a statistically significant difference in adherence, 31% showed that females/women had greater non-adherence, and 20% showed that males/men had greater non-adherence. Figure 2c shows these results stratified by type of adherence problem and ATC group of the medication(s) investigated. Overall, analyses showing no difference in adherence ranged from 36% to 65% among those examining ATC G and unspecified drugs, respectively. Analyses that showed that female participants had greater non-adherence overall ranged from 13% to 60% among those examining ATC P and ATC S (sensory organs) drugs, respectively. Finally, analyses that showed that male participants had greater non-adherence overall ranged from 0% to 30% among those examining ATC P and ATC S drugs, respectively.

Table 2b shows the analytical approaches and results of sex/gender-based analysis of 21 studies that included transgender participants. Overall, 10 studies conducted 11 analyses evaluating differences in adherence between cisgender and transgender participants. Eight studies (80%) compared males/cisgender men with transgender participants and one study (10%) compared males, females, and transgender participants without specifying their sex or gender. One study (10%) treated cisgender and transgender women as a single group in multivariable analysis with cisgender men. Overall, 7 (64%) analyses showed no difference between compared groups, 3 (27%) showed greater non-adherence among transgender women compared to cisgender men, and 1 (9%) analysis showed greater adherence among transgender participants compared to cisgender men.

DISCUSSION

Our review synthesized sex and gender reporting in 937 medication adherence studies among 530,537,287 participants published between 1979 and 2021. A quarter (25%) of included studies considered sex and gender interchangeable variables and most studies (55-64%) used males/females and men/women interchangeably when referring to what should be distinct sex or gender groups. While most analyses (49%) showed no statistical difference in adherence between cisgender participants, those that detected a difference more often reported poorer adherence among females/women (31%) compared to males/men (20%). Poorer adherence among cisgender women compared to cisgender men was most common among studies that examined discontinuation (47% vs 19%) and cost-related non-adherence (37% vs 3%). Very few studies included transgender participants, these studies predominantly examined adherence to drugs for HIV, most did not perform bivariate or multivariate analysis of sex/gender differences, and when difference in adherence were detected, and transgender participants often had poorer adherence than cisgender participants.

It is important to acknowledge obstacles that impede appropriate measurement and analysis of sex and gender in medication adherence research(2). Pharmacoepidemiologic studies often use secondary data from surveys and administrative datasets which regularly do not collect nuanced self-reported measures of these variables, specifically gender and transgender experience(25). As gender is not a singular, quantifiable, and consistent trait but a composite of the effects of relative power, autonomy, poverty, and marginalization within and across populations, challenges in defining gender often preclude its measurement as well as explain why it is often conflated with sex(26, 27). Additionally, observational studies often do not capture reasons for non-adherence which impedes the ability to distinguish whether specific medication problems are a result of sex

(e.g., biological differences in medication effectiveness/safety resulting in non-adherence), gender (e.g., social roles, behaviours, and responsibilities that impede medication taking), or some combination of both. In line with research in social neuroendocrinology demonstrating how mood states, social interactions, and status differentials affect neuroendocrine production and function which in turn may affect behaviour(28, 29), some experts have argued that sex as a biological variable in human studies is inevitably a mix of sex and gender (26, 30-32). Nonetheless, these findings do not preclude the inclusion of distinct dimensions of sex and gender in pharmacoepidemiologic research but rather supports intersectional approaches to examining health inequities that recognize the complex and multiplicative means by which dimensions of social status (e.g., disability, gender, race, socioeconomic status, and sexuality) affect health outcomes(31, 32).

Our scoping review indicates several areas of improvement for pharmacoepidemiologic studies of medication adherence. Foremost, institutions that develop and manage routinely collected surveys and administrative datasets used by researchers need to ensure they use empirical methods of inquiring about sex, gender, and transgender experience as well as provide distinct and expanded response options for these variables that are inclusive of diverse gender identities(33). Consequently, researchers need to appropriately define measures of sex and gender among available data, particularly those using secondary datasets. Notably, we found that 36% of included studies that reported on gender did so incorrectly, as they used medical and administrative data sources that likely only contained information on participants' birth-assigned sex. As administrative data sources contain a narrow range of variables on the social determinants of health (e.g., age, sex, neighbourhood income band), research using these data sources is often 'gender blind' as it is limited to assessing biological and physiological endpoints of disease (e.g., morbidity,

mortality, health services use)(34). While birth-assigned sex is an insufficient measure of biological mechanisms that may affect drug efficacy and safety and, therein, medication taking, it is equally an inappropriate proxy for gender, as it is incapable of capturing social, political, and economic forces that affect health(34). Limitations in available sex and gender measures also exist among secondary survey data that have not updated their data collection practices in accordance with contemporary gender theory(33). Several research methods have been proposed for creating a gender index to capture individual level gender characteristics using available gender-related variables (e.g., occupation, income, labor force participation, unpaid housework, unpaid child/elder care, etc.)(2, 26, 35-37). For researchers administering their own data collection, there is a growing number of resources available for developing and employing theory-driven intersectional measures of sex and gender(33, 38).

While defining and measuring sex and gender are necessary, it is equally imperative to consider potential mechanisms of association between these variables. In a recently published paper, Colineaux *et al.*(39) summarized two analytical strategies for examining mechanisms of health difference between distinct sex and gender groups. Overwhelmingly, pharmacoepidemiologic studies of medication adherence have used a causal framework that conceptualized gender as a phenomenon that occurs at the individual level (e.g., measured as self-reported gender identity, personality inventories, or a composite score of gender-related characteristics) and is influenced by normative social and cultural pressures of having various gendered characteristics according to an individual's birth-assigned sex(39). In this case, mechanisms of interaction between sex and gender are ideally tested through mediation analysis of proposed pathways defined a priori(26, 39). While some studies in our review tested effect modification by sex/gender of a particular exposure of interest on adherence, none examined statistical interactions between sex and gender. Instead,

differential analysis involved examining between group (e.g., summary measures of adherence disaggregated by sex/gender, bivariate/multivariable analysis with a sex/gender covariate) and within group variations (e.g., multivariable analysis stratified by sex/gender) using a single sex or gender measure(26, 32). The reporting of sex disaggregated data has become increasingly more common; however, disaggregating data by male and female promotes a binary understanding of sex that often equates it to gender, suggests broad generalizations across sex/gender groups, ignores intersectional relationships between sex, gender, and other social determinants of health, and excludes intersex, transgender, and gender diverse individuals(26, 32, 34). Bivariate and multivariable analysis that includes a sex/gender covariate provide more information about variations between groups; however, these methods may obscure within group differences. Stratified multivariable analysis provides information on within group determinants; however, this method does not indicate to what extent observed differences between groups are due to chance. All in all, while each of these methods provides valuable information, none alone is sufficient in capturing how sex and gender influence health behaviour, access, and outcomes(26, 32, 34). An alternative strategy proposed by Colineaux *et al.*(39) that is absent from the medication adherence literature is to examine gender as a population level mechanism resulting from an interaction between sex and social environment to account for the heterogeneous and systemic nature of socio-cultural characteristics of populations(39). As institutions and researchers work to improve how sex and gender are examined in pharmacoepidemiologic studies, it is apparent that we must also call to question the limitations of centering a biomedical model of disease that views health problems on the individual level through a single exposure–single disease paradigm to be able to examine population level analytic strategies that address the interdependent social and biological processes that shape public health(40, 41).

Strengths and limitations of our review warrant discussion. A research librarian aided in executing a comprehensive search of published studies; however, as our search was intended to capture sex and gender reporting, it may present a more favourable characterisation of sex and gender inclusion among medication adherence research than is the reality. We used established definitions for three types of problems of medication non-adherence by the European Society for International Society for Medication Adherence(24) as well as the ATC drug classification system which strengthened the applicability of our findings. Our eligibility criteria were restricted to studies published in English as linguistic differences in the conception of sex and gender impeded multilingual synthesis; however, this potentially limited the scope of our review. Finally, we did not have access to data collection tools used by researchers and thereby were not able to systematically evaluate the accuracy and appropriateness of the variables and terms reported by study authors.

Our review provides a comprehensive assessment of sex and gender reporting in studies of medication adherence, one of the most widely studied problems within the field of in pharmacoepidemiology. Altogether, our synthesis revealed inconsistent and insufficient sex and gender considerations, a paucity of research among transgender individuals, and substantial sex/gender disparities in medication taking with studies reporting greater medication adherence problems among cisgender women and transgender participants compared to cisgender men. With growing recognition of the importance of considering both sex and gender in health research, it's essential that researchers work to ensure consistent, appropriate, and responsible sex and gender-based analysis of medication adherence as well as explore new methodologies to account for the diverse, nuanced, and intersectional dimensions of gender within pharmacoepidemiologic research.

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TABLES

Table 1. Study characteristics.

Characteristic		
Study design, n (%)	N= 937	
Cross-sectional	441	(47)
Retrospective cohort	351	(37)
Prospective cohort	124	(13)
Case-control	18	(2)
Nested case-control	2	(<1)
Prospective case series	1	(<1)
Length of study[a], n (%)	N= 838	
Less than 1 year	294	(35)
1 year	147	(18)
2 years	97	(12)
3 to 5 years	175	(21)
5 to 10 years	88	(10)
More than 10 years	40	(5)
Method of adherence measurement[b], n (%)	N= 937	
Self-report	501	(53)
Medical records or claims data	412	(44)

Electronic monitoring	22	(2)
Counts	18	(2)
Blood serum/urine analysis	17	(2)
Type of adherence problem[b], n (%)	N= 937	
Non-initiation	20	(2)
Poor implementation	369	(39)
Discontinuation	237	(25)
Cost-related non-adherence	16	(2)
Nonspecific[c]	375	(40)
Geographic region of study sample[b], n (%)	N= 936	
North America	309	(33)
Asia	240	(26)
Europe	240	(26)
Africa	106	(11)
South America	33	(4)
Oceania	26	(3)
Medications by ATC grouping[b], n (%)	N= 937	
A – Alimentary tract and metabolism	137	(15)
B – Blood and blood forming organs	60	(6)
C – Cardiovascular system	221	(24)

D – Dermatologicals	12	(1)
G – Genitourinary system and sex hormones	19	(2)
H – Systemic hormonal preparations[d]	7	(1)
J – Anti-infectives for systemic use	221	(24)
L – Antineoplastic and immunomodulating agents	122	(13)
M – Musculoskeletal system	36	(4)
N – Nervous system	106	(11)
P – Antiparasitic products, insecticides, and repellents	7	(1)
R – Respiratory system	49	(5)
S – Sensory organs	22	(2)
V – Various	7	(1)
Unspecified	31	(3)
Number of study samples, n (%)	N= 937	
1	919	(98)
2	7	(1)
3	5	(1)
4	1	(<1)
6	1	(<1)
8	3	(<1)
22	1	(<1)

Sample size[a], n (%)	N=1001	
Less than 100	79	(8)
100 to 1,000	501	(50)
1,000 to 10,000	240	(24)
10,000 to 100,000	134	(13)
More than 100,000	47	(5)

[a]Missing data for length of study period (n=99) and sample size (n=3).

[b]Cumulative percentage may be greater than 100, as multiple categories may be relevant to each study.

[c]Included studies that reported an overall adherence measure based on validated or researcher created questionnaires that did not assess a particular problem of adherence (i.e., non-initiation, poor implementation, discontinuation, or cost-related non-adherence).

[d]Excluding sex hormones and insulin.

Table 2a. Sex and gender variable inclusion and categories used to describe participants in studies that included transgender individuals.

Author	Year	ATC group	Data source(s)	Included variable(s)	Language used to describe sex/gender variable group(s) in original publication[a]			
Kalichman(42)	2020	J	Self-report	Gender	Male Man	Female Woman	Transgender man	Transgender woman
Mimiaga(43)	2020	J	Self-report	Gender	Cisgender man	Cisgender woman	Transgender man (female to male)	Transgender woman (male to female)
Hadaye(44)	2020	J	Self-report, pill count	Sex	Male	Female	Transgender[b]	
Kurlander(45)	2019	A	Self-report	Gender	Male	Female Woman	Transgender[b]	

Zablotska(46)	2019	J	Medical records	Gender	Male Man	Female Woman	Transgender female to male	Transgender male to female
Glynn(47)	2019	J	Self-report	Gender	Cisgender male Man	Cisgender female Cisgender woman	Transgender male	Transgender female
Krakower(48)	2019	J	Medical records	Sex and gender	Cisgender male Male Cisgender man Man	Cisgender female Female	Transgender male or trans-masculine identifying	Transgender female or trans-feminine identifying Transgender woman
Pina(49)	2018	J	Self-report	Gender	Male Man			Transgender woman

Hojilla(50)	2018	J	Blood serum analysis	Sex at birth and gender	Man		Transgender woman
Lal(51)	2017	J	Self-report, blood serum analysis, medical records	Gender	Cisgender man	Transgender[b]	
Hoagland(52)	2017	J	Blood serum analysis	Sex and gender	Male Man		Transgender woman
Braun(53)	2017	J	Self-report	Sex and gender			Transgender woman
Mizuno(54)	2017	J	Self-report	Sex at birth and gender identity			Transgender male to female

								Transgender woman
Kalichman(55)	2017	J	Pill count	Sex at birth and gender identity	Male Cisgender man	Female Cisgender woman		Transgender woman
Bogart(56)	2016	J	Electronic monitoring	Gender	Male Man	Female Woman		Transgender male to female
Mehrotra(57)	2016	J	Blood serum analysis	Gender	Cisgender man Man			Transgender woman
Pellowski(58)	2016	J	Self-report, pill count	Gender	Male Man	Female Woman	Transgender[b]	
Pellowski(59)	2016	J	Self-report, pill count	Gender	Male Man	Female Woman	Transgender[b]	

Van den Berg(60)	2016	J	Self-report	Gender	Male Man	Female	Transgender[b]
Beer(61)	2014	J	Self-report	Gender	Male Man	Female Woman	Transgender[b]
Hanif(62)	2013	J	Self-report	Gender	Male Man	Female Woman	Transgender[b]

[a]Some of the terminology listed here is not consistent with current evidence-based descriptions of transgender identities. Researchers should consult up-to-date practice guidelines for ethically and appropriately including transgender participants in health research.

[b]Authors did not specify participants sex or gender.

Table 2b. Results of sex and/or gender-based analysis that included transgender individuals.

Author	Year	Types of non-adherence	Included variable(s)	Method of analysis	Results
Kalichman(42)	2020	Non-specific	Gender	NA	
Mimiaga(43)	2020	Poor implementation	Gender	NA	
Hadaye(44)	2020	Non-specific	Sex	Bivariate: male, female, and transgender[b] participants	No difference
Kurlander(45)	2019	Discontinuation	Gender	Multivariable: cisgender male vs transgender[b] participants	No difference
Zablotska(46)	2019	Poor implementation	Gender	NA	
Glynn(47)	2019	Non-specific	Gender	Multivariable: cisgender males/men vs. cisgender females/women & transgender females group	No difference

Krakower(48)	2019	Discontinuation	Sex and gender	Multivariable: cisgender males/men vs transgender male	No difference
				Multivariable: cisgender males/men vs transgender females/women	Greater adherence among cisgender males/men participants
Pina(49)	2018	Poor implementation	Gender	Bivariate: males/men and transgender women	No difference
Hojilla(50)	2018	Poor implementation	Sex at birth and gender	Multivariable: men vs transgender women	Greater adherence among men
Lal(51)	2017	Poor implementation	Gender	NA	
Hoagland(52)	2017	Poor implementation	Sex and gender	Bivariate: males/men vs transgender women	No difference
Braun(53)	2017	Non-specific	Sex and gender	NA	

Mizuno(54)	2017	Poor implementation	Sex at birth and gender identity	NA	
Kalichman(55)	2017	Poor implementation	Sex at birth and gender identity	Bivariate: males/cisgender men vs transgender women	Greater adherence among males/cisgender men
Bogart(56)	2016	Poor implementation	Gender	NA	
Mehrotra(57)	2016	Poor implementation	Gender	NA	
Pellowski(58)	2016	Poor implementation	Gender	NA	
Pellowski(59)	2016	Poor implementation	Gender	NA	
Van den Berg(60)	2016	Non-specific	Gender	NA	

Beer(61)	2014	Non-specific	Gender	Multivariable: males/men vs transgender[b] participants	No difference
Hanif(62)	2013	Non-specific	Gender	Multivariable: males/men vs transgender[b] participants	Transgender participants were 100% adherent

[a]Some of the terminology listed here is not consistent with current evidence-based descriptions of transgender identities. Researchers should consult up-to-date practice guidelines for ethically and appropriately including transgender participants in health research.

[b]Authors did not specify participants sex or gender.

FIGURE LEGENDS

Figure 1. Sex and gender variable reporting in included studies.

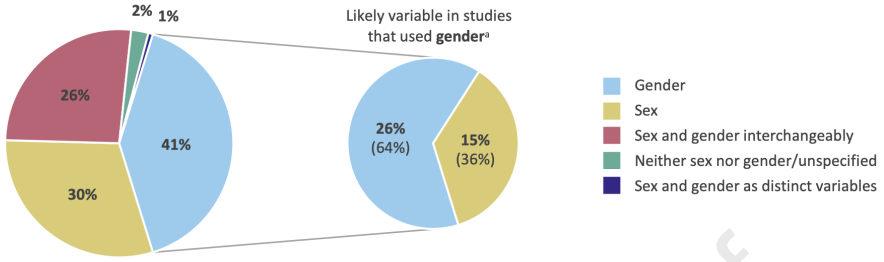
[a]Includes studies that reported using gender but used data sources (e.g., medical records, insurance claims, etc.) that likely only collected data on participants' birth-assigned sex.

Legend: A – Alimentary tract and metabolism; B – Blood and blood forming organs; C – Cardiovascular system; D – Dermatologicals; G – Genitourinary system and sex hormones; H – Systemic hormonal preparations; J – Anti-infectives for systemic use; L – Antineoplastic and immunomodulating agents; M – Musculoskeletal system; N – Nervous system; P – Antiparasitic products, insecticides, and repellents; R – Respiratory system; S – Sensory organs; V – Various; U – Unspecified

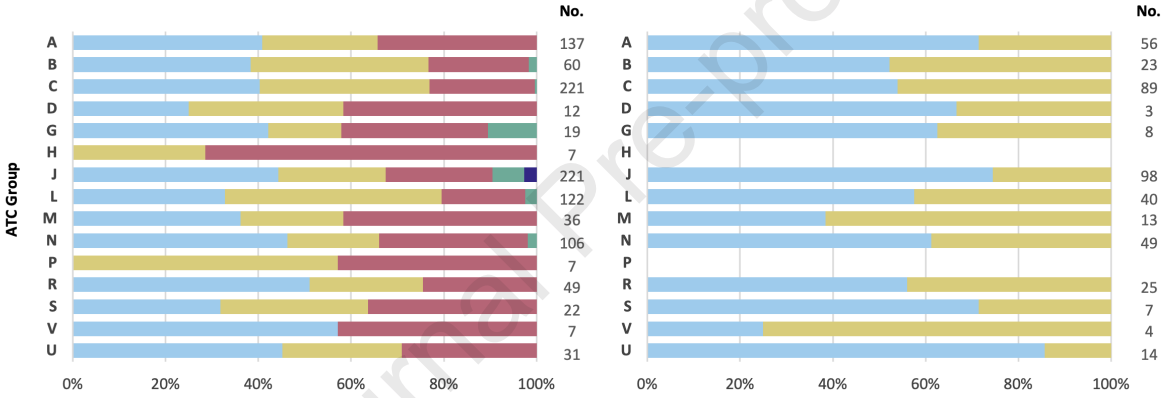
Figure 2. Assessment and results of sex/gender-based analysis of medication adherence among cisgender participants in included study samples.

[a]Cumulative frequency may be greater than the total number of studies represented (N) as multiple categories may be relevant to each study.

Legend: A – Alimentary tract and metabolism; B – Blood and blood forming organs; C – Cardiovascular system; D – Dermatologicals; G – Genitourinary system and sex hormones; H – Systemic hormonal preparations; J – Anti-infectives for systemic use; L – Antineoplastic and immunomodulating agents; M – Musculoskeletal system; N – Nervous system; P – Antiparasitic products, insecticides, and repellents; R – Respiratory system; S – Sensory organs; V – Various; U – Unspecified

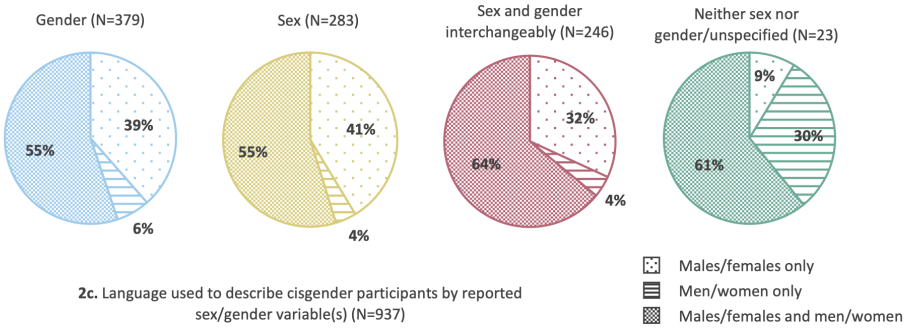


2a. Sex and gender variable(s) reported in observational studies of medication adherence (N=937)

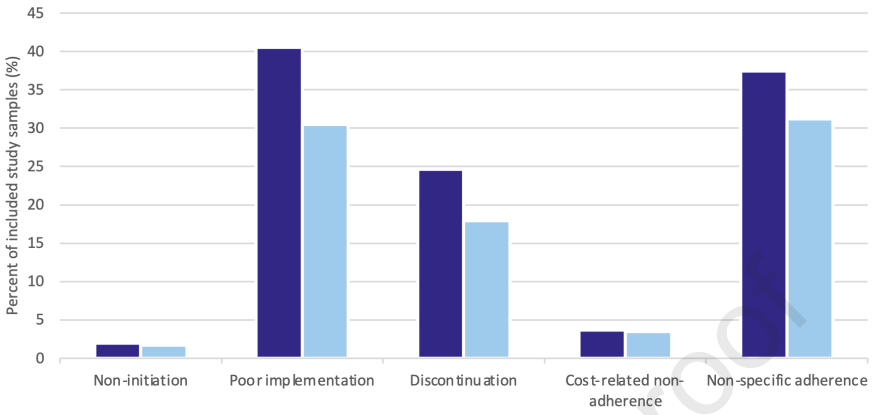


2b. Sex and gender variable(s) reported in observational studies of medication adherence by ATC group (N=937)

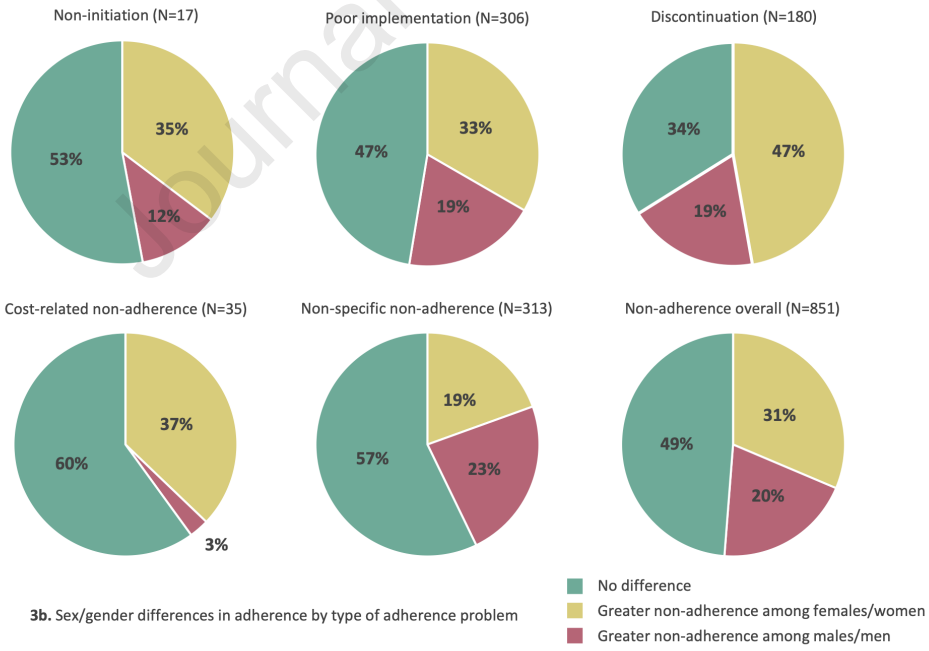
Likely variable in studies that used **gender** stratified by ATC group (N=379)[a]



2c. Language used to describe cisgender participants by reported sex/gender variable(s) (N=937)



3a. Sex/gender-based analysis of adherence among study samples (N=1004)



3b. Sex/gender differences in adherence by type of adherence problem

Table S1a. Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to Feb 03, 2021.

Line	Searches	Results
1	exp Medication Adherence/	20235
2	(adher* or non-adher* or nonadher* or complian* or non-complian* or noncomplian* or medication taking or non-initiation).ti,kf.	72144
3	((medication* or drug* or prescription*) adj3 (adher* or nonadher* or non-adher* or complian* or non-complian* or noncomplian* or persistence or non-persistence or non-initiation or discontinu* or implementation or interrupt* or continuation)).mp.	53171
4	medication taking.mp.	913
5	or/1-4	107382
6	Sex Factors/	268568
7	(sex or gender).mp.	1110381
8	((men and women) or transgender* or intersex or trans gender* or transwomen or transmen or trans women or trans men).mp.	307101
9	(male* and female*).tw,kf.	495182
10	or/6-9	1563840
11	Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy*.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/	3163257
12	(observational or run-in or administrative data).mp.	258859
13	exp "Surveys and Questionnaires"/	1069325
14	or/11-13	3884668
15	exp pharmacologic actions/	8219197
16	(drug* or medication* or prescription* or prescribed).mp.	6253520
17	or/15-16	10043344
18	5 and 10 and 17	7445
19	5 and 10 and 14 and 17	4451

20	limit 19 to (english or french)	4296
21	remove duplicates from 20	4276
21	remove duplicates from 20	4276

Table S1b. Database(s): Embase 1974 to Feb 03, 2021.

Line	Searches	Results
1	exp medication compliance/	34269
2	(adher* or non-adher* or nonadher* or complian* or non-complian* or noncomplian* or medication taking or non-initiation).ti,kw.	109662
3	((medication* or drug* or prescription*) adj3 (adher* or nonadher* or non-adher* or complian* or non-complian* or noncomplian* or persistence or non-persistence or non-initiation or discontinu* or implementation or interrupt* or continuation)).tw,kw.	69697
4	medication taking.tw,kw.	1338
5	or/1-4	171214
6	sex factor/	9411
7	(sex or gender).tw,kw.	1244601
8	((men and women) or transgender* or intersex or trans gender* or transwomen or transmen or trans women or trans men).tw,kw.	422664
9	(male* and female*).tw,kw.	752932
10	or/6-9	2019607
11	exp case control study/ or cohort analysis/ or case control.tw. or (cohort adj (study or studies)).tw. or cohort analy*.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or longitudinal study/ or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional study/ [sign filter]	2685116
12	(run-in or administrative data).tw,kw.	29602
13	11 or 12	2707896
14	5 and 10 and 13	6785
15	limit 14 to conference abstracts	2649
16	14 not 15	4136
17	limit 16 to (english or french)	3982
18	remove duplicates from 17	3906
19	(drug* or medication* or prescription* or prescribed).mp.	11707254
20	18 and 19	2994

Line	Searches	Results
S1	(MH "Medication Compliance")	20,923
S2	TI adher* or non-adher* or nonadher* or complian* or non-complian* or noncomplian* or medication taking or non-initiation	32,151
S3	((medication* or drug* or prescription*) n3 (adher* or nonadher* or non-adher* or complian* or non-complian* or noncomplian* or persistence or non-persistence or non-initiation or discontinu* or implementation or interrupt* or continuation))	31,877
S4	"medication taking"	509
S5	S1 OR S2 OR S3 OR S4	53,494
S6	(MH "Sex Factors")	116,893
S7	sex or gender	335,122
S8	((men and women) or transgender* or intersex or "trans gender*" or transwomen or transmen or "trans women" or "trans men"	104,900
S9	TI (male* and female*) OR AB (male* and female*)	93,974
S10	S6 OR S7 OR S8 OR S9	439,530
S11	(MH "Case Control Studies+") OR (MH "Cross Sectional Studies")	281,743
S12	(MH "Prospective Studies+")	462,260
S13	"case control" or (cohort n1 stud*) or (cohort analys*) or ("follow up" n1 stud*) or (observational n1 stud*) or longitudinal or retrospective or "cross sectional" or "run in" or "administrative data"	819,118
S14	(MH "Surveys+")	234,368
S15	S11 OR S12 OR S13 OR S14	1,243,302
S16	(drug* or medication* or prescription* or prescribed)	1,043,583
S17	S5 AND S10 AND S15 AND S16	1,724
S18	S5 AND S10 AND S15 AND S16	1,634

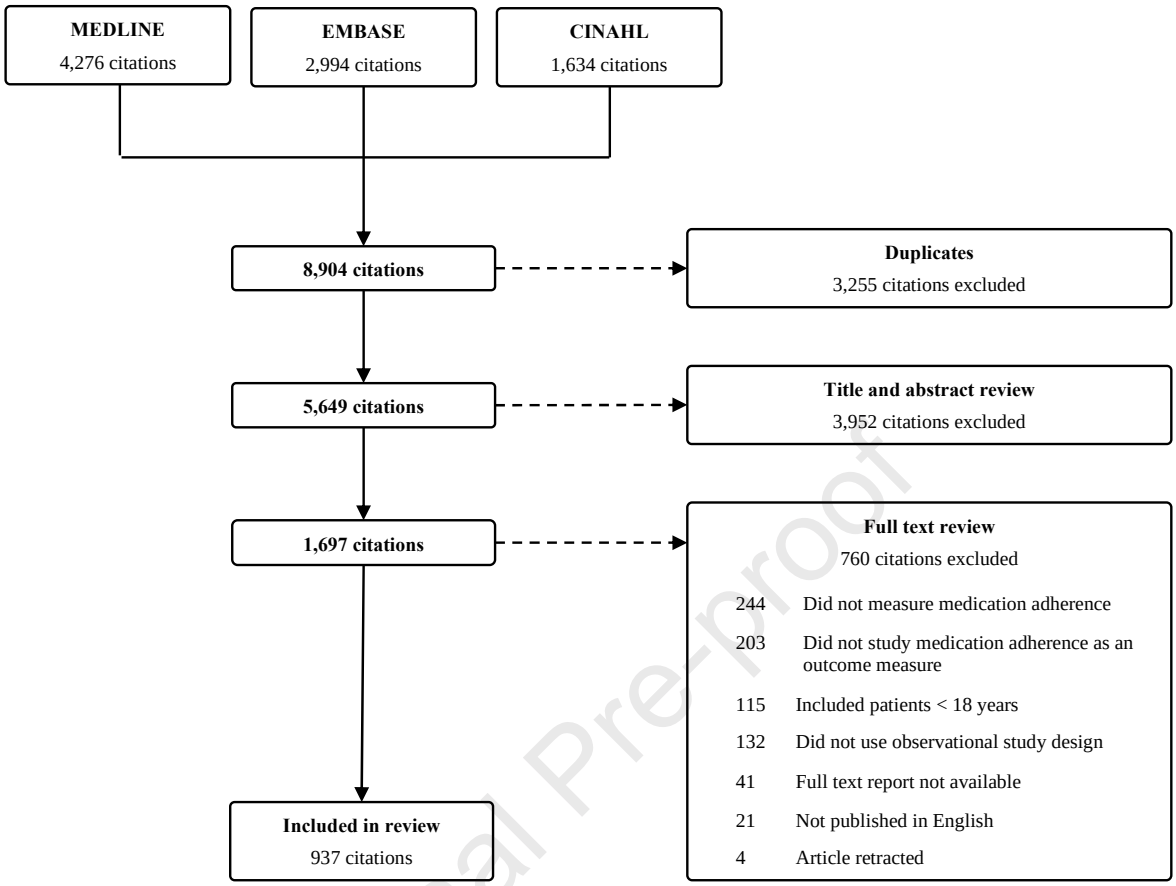


Figure S1. Selection of included studies.

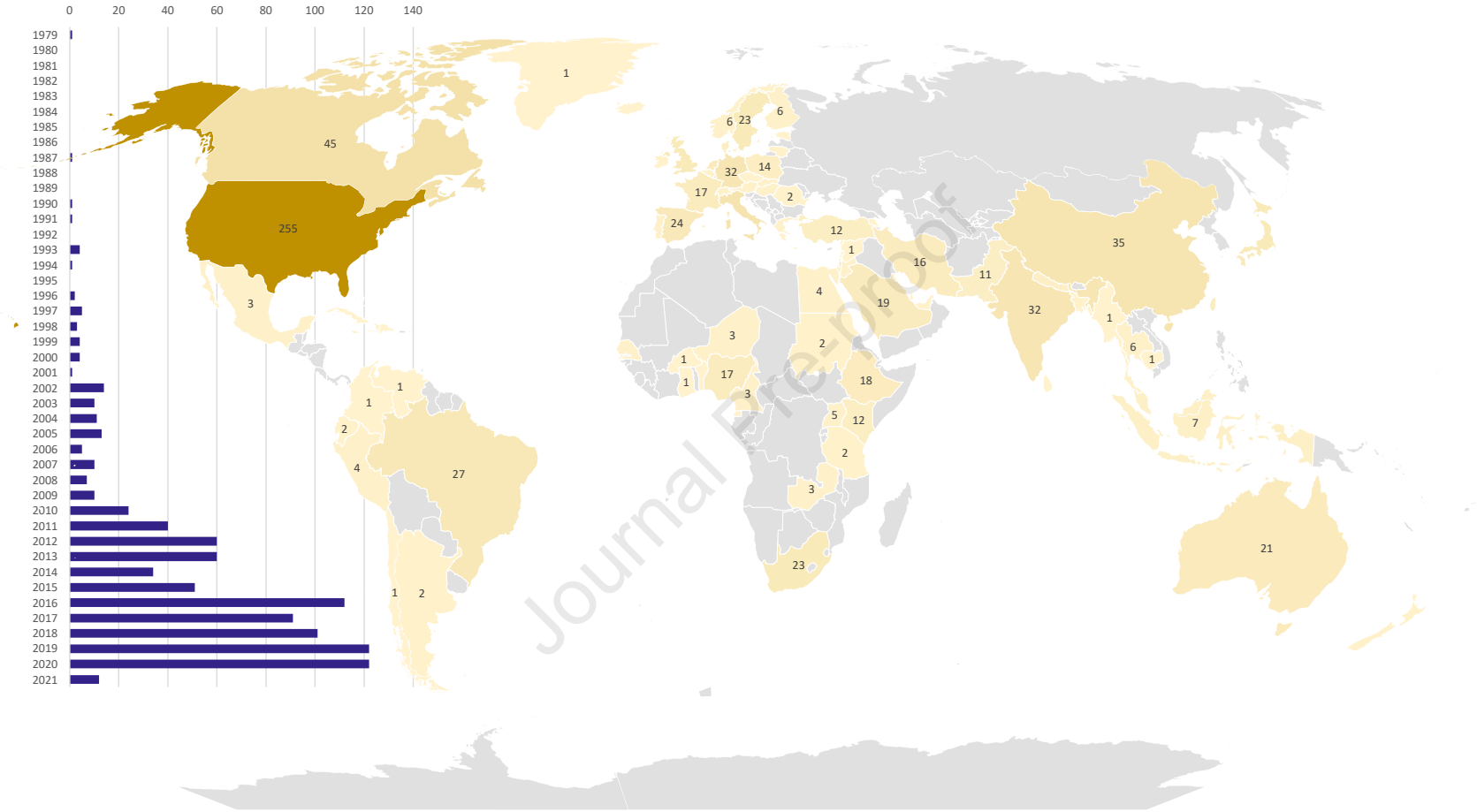


Figure S2. Frequency of studies published by year and country.