

Research Article

Medication Non-Adherence Identified at Home: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Patients dwelling at home are at risk of medication non-adherence which is directly associated with poor treatment outcomes. This study aimed to estimate the prevalence rate of medication non-adherence occurring at patient's home.

Methods: EMBASE, PUBMED/MEDLINE, SCOPUS and CINAHL were searched from their inceptions to January 2016. Original articles were included if they enrolled patients home domiciled and provided sufficient data for calculating the prevalence. The quality assessment of included studies was performed using Crombie's items. Pooled estimates were obtained by using random-effect model. STATA was used for data analysis.

Results: Of 3398 articles identified, 13 met the inclusion criteria. The median prevalence of medication non-adherence detected in home settings was 38.6% [Interquartile range (IQR): 12.8-53%]. According to population, the median prevalence in elderly was 43.2% (IQR: 13.2-57.7%) whereas that in all-

aged population was 8.4% (95% CI, 6.3-10.5%; χ^2 0.61; d.f.1; $I^2=0\%$; $p=0.435$). Using pill count as a method of detection showed the highest medication non-adherence rate (70%, 95% CI; 61-79%). High income countries reported a higher levels of non-adherence to medications (median 46.8%, IQR: 26.4-57.7%) than lower middle-income countries (9.6%, 95% CI; 5.7-13.5%) or upper middle-income countries (8.4%, 95% CI; 6.3-10.5%; χ^2 0.61; d.f.1; $I^2=0\%$; $p=0.435$). Medication involving cardiovascular, alimentary tract and metabolic and respiratory diseases were most implicated with non-adherence.

Conclusion: Non-adherence to medication detected at patients' home was appreciable. Healthcare professional should be aware of adherence problems in community and further design an effective strategy for improving adherence to achieve desired therapeutic outcomes and safety.

Keywords: Home; Patient adherence; Patient compliance; Non-adherence; Non-compliance

How this fits in with quality in primary care?

What do we know?

Patients dwelling in their own homes or in community are vulnerable to have medication non-adherence because many are elderly and unsupervised. No systematic review and meta-analysis estimated the extent of this issue.

What does this paper add?

Medication non-adherence is evidently considerable in primary care settings with two in five patients dwelling in home encountered this problem, particularly in the elderly population. Cardiovascular treatments are most commonly subject to medication non-adherence and clinicians in primary care should monitor adherence closely in patients at home.

Abbreviations: AHRQ: Agency for Healthcare Research and Quality; ATC: Anatomical Therapeutic Chemical; CI: Confidence Interval; CINAHL: Cumulative Index to Nursing and Allied Health Literature; IQR: Interquartile Range

Introduction

The term 'medication adherence' is defined as the extent to which patient behavior in taking medication, a diet and/or executing lifestyle changes, accord with recommendations with health care providers [1]. Patients not adhering to their medications has been a crucial problem in pharmacotherapy and occurred at any stage of their treatment. Medication non-adherence also causes poor treatment outcomes, poor quality

of life, and subsequent hospitalization and emergency room visits [2-4]. Apart from negative clinical outcomes, medication non-adherence further burdens healthcare systems and their resources. In the United States, spends \$100 and \$300 billion annually was attributable to non-adherence to medication, accounting for 3-10% of national health care budget [5], while the EU devotes €125 billion annually for this purpose [6].

Patients at home are vulnerable to medication non-adherence because (i) they live in an uncontrolled environment compared to that in hospitals, (ii) consume multiple medications both prescriptions and over the counter drugs, (iii) and little supervision at home [7]. The consequential non-adherence results in adverse outcomes and hospital admissions [8].

Many studies have assessed non-adherence of home domiciled patients, however, no systematic review has been conducted on this issue. Accordingly, this study aimed to quantify prevalence and nature of non-adherence to medications within domiciled settings.

Methods

Search strategy

A systematic search of PUBMED/MEDLINE, SCOPUS, EMBASE and CINAHL since their inception to January 2016 using keywords or of their synonyms: (“drug-related problem” OR “medication-related problem” OR “adherence” OR “compliance”) AND “home setting”. In addition, bibliographies of included articles were also screened for relevant studies.

Eligibility criteria

Original studies were included if they enrolled patients dwelling at home and reported the prevalence of medication non-adherence. Investigations in hospital settings or long-term care facilities or focusing on specific medications or medication groups were excluded.

Study selection and data extraction

The retrieved articles were screened independently by 2 investigators (P.M. and C.K.) against a pre-specified selection criteria. The studies meeting the eligibility criteria were then extracted using a standardized form. Information to be extracted were as follows: study characteristics (study design, setting, year, sample size), study population (age, sex), method used to measure non-adherence, prevalence rates of non-adherence to medications. Medications involved in non-adherence were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [9]. We also contacted authors for raw data if necessary. Any disagreement was discussed until a consensus was reached.

Quality assessment of studies

The risk of bias of eligible studies was assessed using Crombie’s items which contain 7 criteria for quality of cross-sectional/prevalence studies as recommended by the Agency for Healthcare Research and Quality (AHRQ) [10]. In brief, 7-categories include (i) appropriate design, (ii) adequate description of data, (iii) report response rates, (iv) adequately represent the total sample, (v) clearly stated aims and likelihood of reliable and valid measurements, (vi) statistical significance, and (vii) adequate description of analyses. Articles were given quality scores ranging from 0-7. All disagreements were resolved by discussion.

Data analyses

Prevalence rates were expressed as the ratio of numbers of non-adhering patients to total patients, and these outcome measures were used for statistical pooling. The pooled prevalence and 95% confidence interval (95% CI) were derived using the random-effects model of the Dersimonian–Laird method assuming that the true effect size varies between studies [11]. To assess heterogeneity of prevalence rates among studies, we

used standard χ^2 tests, and the I^2 statistic. If I^2 75%, considerable heterogeneity is indicated and, median prevalence [interquartile range (IQR)] was reported instead of pooled estimates (95%CI). To explore potential heterogeneities, the average estimate was stratified by age group, i.e., “elderly” (>60 years) or “all age groups”, method for assessing medication non-adherence (“pill count”, “combination of pill count and interview”, “self-report”, “interview” and “case review”) and socio-economic status (“high income countries”, “upper middle-income countries” and lower middle-income countries”). All analyses were performed using STATA, v14.1 [12].

Results

Search results

Of 3398 articles identified from the databases searches, 738 duplicates were removed. After screening the title and abstract, some articles were removed: (a) irrelevant to non-adherence to medications (1133 articles); (b) reviews (401); (c) case reports (98) or case series (19); (d) were not human studies (87). The remaining 522 articles were fully assessed for eligibility and 511 were removed because the patients were not home domiciled (506 articles), or contained insufficient data to calculate prevalence rates of non-adherence to medications (5 articles). Two additional articles were identified by hand-searching. Thus, 13 articles [13-25] were included in the systematic review and meta-analysis (Figure 1).

All included studies (n=13) were cross-sectional studies, investigating medication non-adherence detected in patients living at home (Table 1), set in N. America (5 studies), Europe (3), Australia (2), Asia (2) and S. America (1). Five methods were employed to assess medication non-adherence: interview (7 studies), patient self-report via questionnaire (3), case note review (1), residual pill counting (1) and combined method of interview/pill count (1). According to population characteristics, eleven studies were conducted in elderly and three in the ‘all age groups’. Among the studies in the elderly, five studies [13,14,16,17,19] reported that more than 40% of subjects lived alone but not reported in the remainder.

The study qualities by Crombie item scores was 3-7 but 8/13 attracted scores >5 demonstrating good quality (Table 1).

Definition used to assess medication non-adherence

There was a variety of definitions used to determine medication non-adherence in the included studies. Four studies [13,14,21,25] employed a vague criteria described as “patients did not adhere to prescription direction”. Two studies [19,20] judged non-adherence based on Morisky scale. Five studies [17,22,24] defined patients with medication non-adherence if they missed a single dose or failed to take a drug [15-17,22,24] or an extra dose was taken [15,16]. One study [18] used the criteria developed by Strand et al. [26]. One study [23] classified patients as non-adherent if the pill count was lower than 80% or greater than 110% of anticipated pill counts.

Prevalence of non-adherence in home settings

The 13 studies comprised a total of 4072 home residents of whom 995 were identified as non-adherent to medications.

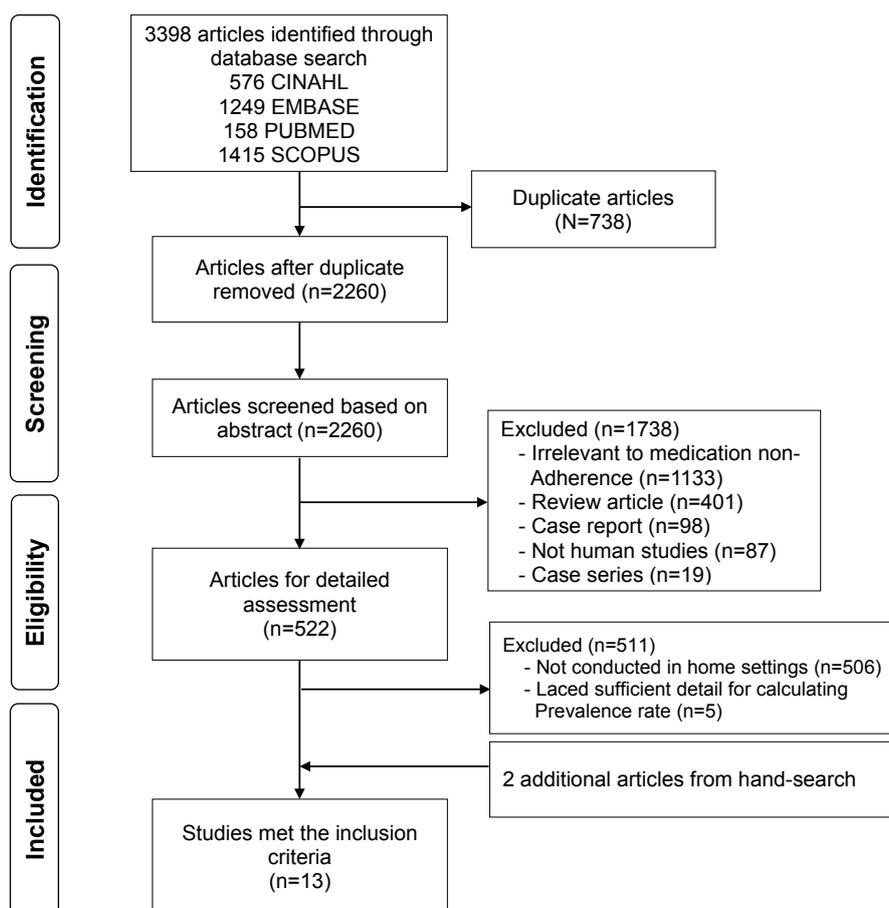


Figure 1: Study selection flow diagram.

Table 1: Characteristics of 13 included studies.

Author	Year of publication	Survey year	Population	Crude rate prevalence (%)	Mean Age (year)	Men (%)	Adherence measure	Setting	Socioeconomic status	Crombie's score
Cooper et al. [13]	1982	NA	Elderly	48/111 (43.2)	70.5	41	Interview	United States	High income country	4.5
Darnell et al. [14]	1986	NA	Elderly	78/155 (50.3)	71.6	28.4	Interview	United States	High income country	4.5
Zeppetella et al. [15]	1999	1995-1997	Elderly	64/111 (57.6)	66.4	55.9	Interview and pill count	United Kingdom	High income country	3
Barat et al. [16]	2001	1998	Elderly	92/348 (26.4)	75	43	Interview	Denmark	High income country	6.5
Thompson et al. [17]	2001	1993-1995	Elderly	163/204 (80.0)	NA	30	Interview	Australia	High income country	5.5
Roughead et al. [18]	2004	NA	Elderly	132/1,000 (13.2)	Median, 74 (M), 75.5 (F)	38	Case note review	Australia	High income country	4
Roth et al. [19]	2005	2002	Elderly	53/100 (53.0)	77.5	15	Self-reported	United States	High income country	6.5
Vik et al. [20]	2006	2000	Elderly	123/319 (38.6)	82.8	21	Self-reported	Canada	High income country	7
Mastroianni et al. [21]	2011	2008	All age group	21/280 (7.5)	NA	NA	Interview	Brazil	Upper income country	5
Fiss et al. [22]	2011	2006-2008	Elderly	95/744 (12.8)	80.5	26.9	Self-reported	Germany	High income country	5.5
Turner et al. [23]	2012	NA	Elderly	70/78 (70.0)	75	26	Pill count	United States	High income country	5
Kumar [24]	2012	NA	Elderly	21/219 (9.6)	NA	NA	Interview	India	Lower income country	NA
Kongkaew et al. [25]	2015	2015	All age group	35/381 (9.2)	56.7	30.18	Interview	Thailand	Upper income country	5.5

Abbreviations: NA: Not Applicable

Crude prevalence rate of medication non-adherence ranged from 7.5% [21] to 80% [17], with a number of population varied from 78 [23] to 1,000 [18]. Across the 13 studies, the median prevalence rate of medication non-adherence was 38.6% (IQR: 12.8-53%; χ^2 1033.2, d.f.12; $I^2=98.8\%$, $p<0.001$).

When sub-grouped by age, the result showed that studies on elderly participants reported a higher prevalence rate (median=43.2%; IQR: 13.2-57.7%; χ^2 905.4; d.f.10; $I^2=98.9\%$, $p<0.001$) than all-age groups (pooled prevalence=8.4%; 95% CI: 6.3-10.5%; χ^2 0.61, d.f.1; $I^2=0\%$, $p=0.435$) (Figure 2). When sub-grouped by measurement methods, medication non-adherence rate was highest by pill-counting (70%; 95%CI, 61-79%), but lower when combining pill-count with interview (57.7%; 95% CI, 48.5-66.8%), by self-report (median=38.6%; IQR: 12.8-53%; χ^2 123.8, d.f.2; $I^2=98.4\%$, $p<0.001$), by interview (median=26.4%; IQR: 9.2-50.3%; χ^2 688, d.f.6; $I^2=99.1\%$, $p<0.001$) and case review (13.2%; 95% CI: 11.1-15.3%). When sub-grouped by socio-economic status, studies originating from high income regions [13-20,22,23] had a higher mean prevalence rate (median=46.8%; IQR: 26.4-

57.7%; χ^2 858.4, d.f.9; $I^2=99\%$, $p<0.001$) than studies conducted in upper middle-income [21,25] (8.4%; 95% CI: 6.3-10.5%; χ^2 0.61, d.f.1; $I^2=0\%$, $p=0.435$) and lower middle-income countries [24] (9.6%; 95% CI: 5.7-13.5%) (Table 2).

Medications involving non-adherence at patients' home

Only 3/13 studies [13,15,16] reported medication classes most associated with medication non-adherence were those treating cardiovascular, alimentary tract and metabolic and respiratory diseases (Table 3).

Discussion

This systematic review reveals that around two-fifth of patients dwelling at home did not adhere to their medication regimens. This was 5-fold higher than non-adherence rates on hospital admissions [27]. In addition, the prevalence rate of medication non-adherence identified in elderly was far greater than in adults (Table 2). Although some studies [28-30] found that younger participants were less adherent with their medication regimens than older people, but our meta-analysis demonstrated more medication non-adherence in the elderly.

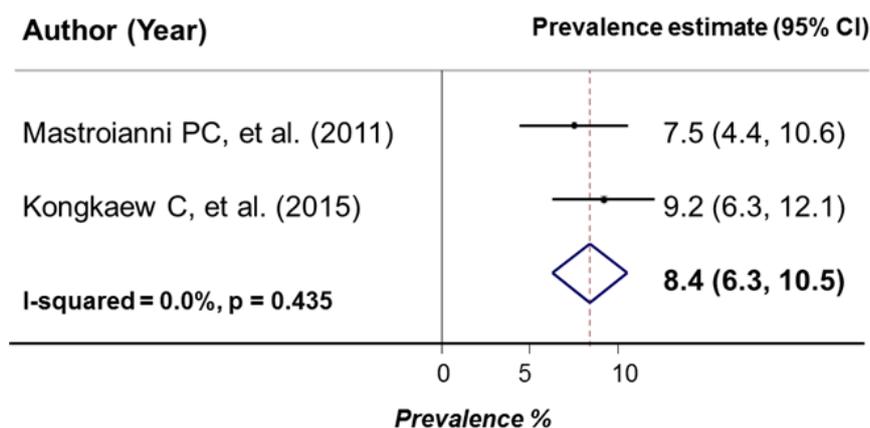


Figure 2: Pooled prevalence of medication non-adherence in all age population.

Table 2: Subgroup analysis according to population, methods of measurement and socioeconomic status.

	No. of study	Prevalence estimate, % (95% CI)	Heterogeneity test			
			χ^2	d.f.	I^2	p-value
Population						
Elderly	11 [13,14,16-20,22-24]	Median 43.2 (IQR; 13.2-57.7)	905.4	10	98.9%	<0.001
All age group	2 [15,21,25]	8.4 (6.3-10.5)	0.61	1	0%	0.435
Method to measure adherence problems	7		688	6	99.1%	<0.001
Interview	[13,14,16,17,21,24,25]	Median 26.4 (IQR; 9.2-50.3)	123.8	2	98.4%	<0.001
Self-reported	3 [19,20,22]	Median 38.6 (IQR; 12.8-53)	NA	NA	NA	NA
Combined method of interview& pill count	1 [15]	57.7 (48.5-66.8)	NA	NA	NA	NA
Case note review	1 [18]	13.2 (11.1-15.3)	NA	NA	NA	NA
Pill count	1 [23]	70 (61-79)	NA	NA	NA	NA
Socioeconomic status						
High income countries	10 [13-20,22,23]	Median 46.8 (IQR; 26.4-57.7)	858.4	9	99%	<0.001
Upper middle income countries	2 [21,25]	8.4 (6.3-10.5)	0.61	1	0%	0.435
Lower middle income countries	1 [24]	9.6 (5.7-13.5)	NA	NA	NA	NA

Abbreviations: CI: Confident Interval; IQR: Interquartile Range

Table 3: Medication classes involved in medication non-adherence classified according to ATC classification system.

Author (year)	Medication class (Individual medication)	No. of events	Percentage (%)
Cooper et al. (1982) [13]	Cardiovascular system (NR)	16/58	27.6
Darnell et al. (1986) [14]	NR	NR	NR
Zeppetella et al. (1999) [15]	Alimentary tract and metabolism (Laxatives)	NR	About 20%
Barat et al. (2001) [16]	Respiratory system (NR)	NR	13% ^a
Thompson et al. (2001) [17]	NR	NR	NR
Roughead et al. (2004) [18]	NR	NR	NR
Roth et al. (2005) [19]	NR	NR	NR
Vik et al. (2006) [20]	NR	NR	NR
Mastroianni et al. (2011) [21]	NR	NR	NR
Fiss et al. (2011) [22]	NR	NR	NR
Turner et al. (2012) [23]	NR	NR	NR
Kumar (2012) [24]	NR	NR	NR
Kongkaew et al. (2015) [25]	NR	NR	NR

Abbreviations: NR: Not Report; ^a: Lower Dose than Prescribed

Several reasons for medication non-adherence among elderly have been proposed. (i) Older people may have poor vision, hearing, and memory, (ii) difficulty in following instructions, opening drug containers, and handing small tables [31], (iii) have inadequate education about the medication, recognizing adverse drug reactions, and competing prescription medications could be a barrier of adherence in older people [32]. Our study also identified that almost 40% of elderly patients in this study lived independently [13,14,16,17,19]. It is noteworthy that elderly who live alone without caretakers were at risk of medication non-adherence [16,33,34]. Thus, in order to increase the adherence rates among elderly, simplified treatment regimens, use reminder devices, and large easily read labels are needed.

Patients dwelling in the community or in their own home are particularly vulnerable for medication non-adherence because they consumed medications without supervision and are often overlooked by health care systems. In our study, the high prevalence of medication non-adherence in such patients provides much scope for improvement. To realize this, it requires continuous processes of identification of barriers to adherence, implementing effective strategies according to individual needs, and close monitoring of adherence. Furthermore, educating patients about their medications, disease, and how to self-monitor adverse events, thereby establishing more trusting relationships between patients and health-care providers as recommended [35,36]. Home-care, support by family members, and follow-up visits could further promote adherence [37,38]. While each factor above may incrementally foster adherence, multiple interventions appear to be more sustainable [39,40].

Our finding also revealed that pill-counts yielded the highest non-adherence rates and is objective, cheap and simple. However, if ideally, the number of pills prescribed and number consumed can be accurately accounted for, those lost to attrition or extra pills taken cannot be assessed thereby risking false

adherence rates. Subjective methods (e.g. interview, self-report or case notes) seem to be popular in clinical practice due to their low cost, simplicity and immediate feedback, but risks under-reporting to please the clinical supervisor [41]. Thus, there is no 'gold standard' to quantify adherence. Multi-measure approach with clear defined treatment outcome is recommended provides estimations closest to reality [41,42] together with measuring ultimate treatment outcomes (e.g. hospital stay, morbidity and mortality rates).

Prevalence of medication non-adherence was greater in high-income countries compared to those studies conducted in upper and middle income countries. This finding may be contrary to some previous studies [43,44] which have suggested that people who had no insurance or low income were more likely to be non-adherent to medication. But even for people with health insurance, their health expenditures could still be a problem as more than 10% of elderly in the USA, for example, used less of their required medication because of cost [45]. Although majority of the included studies was conducted in high-income countries, the estimated prevalence rate might not reflect the situation of non-adherence to medications in all high income countries due to differences of healthcare system. In addition, we also need more studies in other hemisphere to draw a global conclusion. Apart from this, several factors may influence the prevalence rate of adherence including age of population, methods for measuring non-adherence, complexity of medication regimen, medical condition, living condition, gender, level of education and ability for self-care [31].

Drugs attracting non-adherence could be ranked as those treating cardiovascular, alimentary tract and metabolic, and respiratory disease which accords with a previous meta-analysis showing that ~50% of patients taking cardiovascular medications were non-adherent [46] and was associated with increased mortality [47]. Likewise, non-adherence to

medications for gastrointestinal tract, diabetes mellitus, and respiratory conditions had an increased risk of hospitalization and health-care expenditure [5,48,49]. Recent studies suggested that self-management, daily dose regimen and affordable therapies with minimal side-effects combined with effective patient-clinician communication improves medication adherence [50,51].

To our knowledge, this is the first systematic review and meta-analysis examining the extent and natures of medication non-adherence identified at home and have much strength. We applied a thorough search strategies including (i) wide range of well-recognized international bibliographic databases, (ii) hand searching for unpublished articles; and (iii) no languages restrictions. This was to ascertain that the included studies were representative. In addition, our study adheres to standard methodology of systematic review and meta-analysis as indicated by the PRISMA statement [52].

This study has some limitations that might affect the overall estimated prevalence rates. (i) Some missing data in the original included studies (e.g. number of non-adherent patients, their ages), despite our attempts to contact the studies' authors, (ii) there was high heterogeneity between studies and where encountered, the results were summarized using the median rate and interquartile range, instead of a meta-analytic summary. We also need more studies in other hemisphere to draw a conclusion.

The findings from this meta-analysis have important implications. Based on considerable prevalence rate of medication non-adherence for home domiciled patients, healthcare professionals in primary care system should be aware of non-adherence problem occurring at patients' home and closely monitored. Our estimated prevalence rate of medication non-adherence could serve as a point of reference for countries in which prevalence rates of non-adherence in home settings are poorly characterized.

Based on our review, studies examining the prevalence rate of medication non-adherence in children and/or pediatrics and factors that determine adherence to medications in general are lacking. Future study need to investigate these. In addition to the prevalence rate of medication non-adherence, further studies may include ultimate therapeutic outcomes stemmed from medication non-adherence (e.g. adverse outcomes, morbidity and mortality) to gain clear understanding the impact of medication non-adherence.

Conclusion

Non-adherence is clearly a major problem in home domiciled patients particularly in the elderly probably through the combination of polypharmacy, chronic disease, and cognitive decline. Identification of factors associated with medication non-adherence among patients dwelling at home is further needed.

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