AGING & MENTAL HEALTH
2019, VOL. 23, NO. 8, 932–941
https://doi.org/10.1080/13607863.2018.1468411

Routledge
Taylor & Francis Group

Association between polypharmacy and dementia – A systematic review and metaanalysis

Nattawut Leelakanok[a] and Ronilda R. D'Cunha[b]

[a]Faculty of Pharmaceutical Sciences, Burapha University, Chonburi, Thailand; [b]College of Pharmacy, The University of Iowa, Iowa City, IA, USA

ABSTRACT

Objective: The association between polypharmacy and dementia is controversial. This systematic review and meta-analysis aims to summarize existing literature concerning the association between polypharmacy and dementia.

Methods: A systematic literature review was performed by searching the EMBASE, PubMed, Scopus and International Pharmaceutical Abstract databases using terms related to polypharmacy and dementia. A meta-analysis was performed using random effect models.

Results: Seven studies were included in this meta-analysis. The included studies were of medium to high quality with a potential for publication bias. A strong association between polypharmacy and dementia was found (pooled adjusted risk ratio (aRR) = 1.30 (95% CI: 1.16–1.46), $I^2 = 68\%$). Excessive polypharmacy was also strongly associated with dementia (pooled aRR = 1.52 (95% CI: 1.39–1.67), $I^2 = 24\%$).

Conclusion: Pooled risk estimates from this meta-analysis showed that polypharmacy was associated with dementia. Although the causality of the relationship cannot be concluded from this analysis, the finding encourages the use of multidimensional assessment tools for dementia that includes the number of medications as a component.

ARTICLE HISTORY
Received 11 January 2018
Accepted 15 April 2018

KEYWORDS
Polypharmacy;multiple drug use;dementia;Alzheimer's disease

Introduction

Dementia is a clinical syndrome that manifests as a decline in cognitive, emotional and conative functions that are severe enough to impair social and occupational functioning (Chert- kow, Feldman, Jacova, & Massoud, 2013). Although dementia can be caused by multiple disorders that affect brain functions (Emre, 2009), the most general types of dementia are Alzheimer's disease and vascular dementia (Rizzi, Rosset, & Roriz-Cruz, 2014). Because of population aging worldwide, dementia has become a significant global disease burden. According to the World Health Organization, the number of people living with dementia in 2017 was estimated to be 47 million worldwide (Virot, 2017). With this number, we can imply that millions of family caregivers of people with dementia are also affected. Taking care of a family member with dementia leads to physical and psychological stress, social isolation and financial difficulty (Brodaty & Donkin, 2009). In addition, dementia has an extremely significant negative impact on economic status. The global total estimated costs of dementia in 2010 was US $604 billion (Wimo, Jonsson, Bond, Prince, & Winblad, 2013). With this remarkable global impact, it is important to identify protective factors and risks of dementia to reduce its incidence.

Several risk factors of dementia have been identified. Genetics, parental age at birth, female sex, being overweight and obesity, comorbidities such as cardiovascular diseases and diabetes and high blood pressure are associated with a higher risk of dementia (Chen, Lin, & Chen, 2009; McCullagh, Craig, McIlroy, & Passmore, 2001; van der Flier & Scheltens, 2005). Concurrent use of multiple medications is one of the possible risk factors for dementia. In general, the use of five or more drugs at the same time is defined as polypharmacy, although other threshold numbers have been used arbitrarily (Leelakanok, Holcombe, Lund, Gu, & Schweizer, 2017). The other concept is excessive polypharmacy, which is defined as the concurrent use of 10 or more medications (Leelakanok et al., 2017). Several studies supported that polypharmacy has an association with dementia. For example, a case study reported reversible dementia because of polypharmacy (Gupta, Singh, Singh, & Lehl, 2013). In addition, studies found more functional decline (Lau, Mercaldo, Shega, Rademaker, & Weintraub, 2011; Sarkar et al., 2017) and cognitive impairment (del Ser et al., 2005; Fratiglioni, 2011; Monastero, Palmer, Qiu, Winblad, & Fratiglioni, 2007; Silay, Yalcin, Akinci, Gursoy, & Sener Dede, 2017) in patients with polypharmacy. Several studies have also demonstrated that patients with dementia used a higher number of medications (Andersen, Viitanen, Halvorsen, Straume, & Engstad, 2011; Green et al., 2017; Lau et al., 2010; Mate et al., 2015; McCracken, McCormack, McGregor, Wong, & Garrison, 2017) and polypharmacy was more frequent in dementia patients (Kose, Maruyama, Okazoe, & Hayashi, 2016; Ostrom, Hammarlund, Christensen, Plein, & Kethley, 1985; Rattagan et al., 2016). However, some other studies found no association between number of medications and dementia (Gnjidic et al., 2012; Schubert et al., 2006). Some

CONTACT Nattawut Leelakanok nattawut.le@go.buu.ac.th

Supplemental data for this article can be accessed at https://doi.org/10.1080/13607863.2018.1468411.

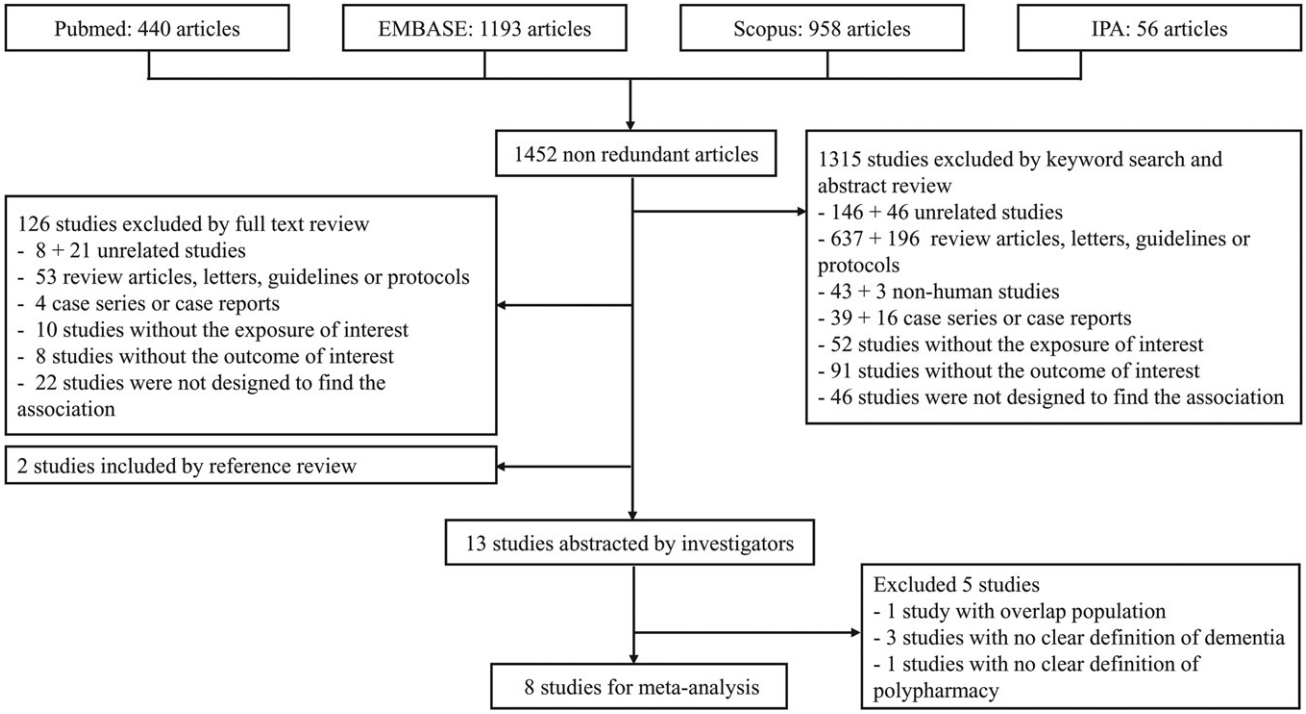

Figure 1. PRISMA diagram for the systemic review of the association between polypharmacy and dementia.

studies even showed that patients with dementia use a lesser number of medications (Gnjidic et al., 2012) and were at lower risk for inappropriate drug use (Cool et al., 2014). This controversy is not surprising because the effects of medications on dementia are diverse. For example, alcohol (Hulse, Lautenschlager, Tait, & Almeida, 2005), anticholinergics (Starr & Whalley, 1994), benzodiazepines (Gomm et al., 2016), estrogen (Shumaker et al., 2004) and proton pump inhibitors (Gomm et al., 2016; Haenisch et al., 2015) are reported to be associated with higher risk of dementia while metformin (Ork- aby, Cho, Cormack, Gagnon, & Driver, 2017), HMG-CoA reductase inhibitors and nonsteroidal anti-inflammatory drugs (Chen et al., 2009) can lower the risk of dementia.

With conflicting evidence on the potential of polypharmacy to be a risk factor of dementia, this systematic review and meta-analysis attempts to summarize the existing literature investigating the association between polypharmacy and dementia. Our primary objective is to define the summary statistics concerning the association between polypharmacy and dementia. The secondary objective is to investigate the association between excessive polypharmacy and dementia.

Methods

Data source and search strategy

Search terms were defined and a systematic literature search was performed by the first author using MEDLINE/PubMed, EMBASE, Scopus and International Pharmaceutical Abstract (IPA) from inception to 1st October 2017 using the terms polypharmacy (e.g. multiple drug used) AND dementia (e.g. Alzheimer's disease) without applying time, language or study design restrictions. The MEDLINE database was searched through PubMed by using Medical Subject Headings (MESH) and Text Words (TW). EMBASE was searched using Emtree terms and synonyms. Full search strategies are provided in the Electronic Supplementary Material 1. Potential related studies were also searched from references of review articles and relevant excluded studies.

Inclusion and exclusion criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist was used for this systematic review and meta-analysis. Studies were included in this metaanalysis if they were (i) human studies conducted in older population (>65 years of age), (ii) studies that defined polypharmacy as multiple medication use, and (iii) studies that indicated dementia as an outcome. Studies were excluded if they were (i) review articles, (ii) case reports or case series, (iii) studies with data that could not be used to calculate risk ratios, (iv) studies that did not provide the definition of polypharmacy. Rationale for the exclusion criteria is provided in the Electronic Supplementary Material 2. The PRISMA diagram of the systematic literature search and review process is shown in Figure 1.

Data abstraction

Articles retrieved from searching were stored in a citation manager (EndNote X7, Thomson Reuters, New York, USA). Redundant articles, titles and abstracts of the rest of the articles which were reviewed by the first author by searching for specific words for exclusion (e.g. to exclude non-human studies, words such as mice and *in vitro* were searched) were removed. The remaining abstracts were reviewed. For nonEnglish articles, English abstracts and result sections in full texts were used to determine if further translation would be necessary. For the abstraction process, the abstraction form was designed by the first author and reviewed by the second author. Information on study design, location, patient demographics, polypharmacy definition, and potential confounders in every study

Table 1. Description of included studies.

Author	Study design	Location and year of study	Demographics	Polypharmacy (exposure)	Dementia (outcomes)	Confounder adjusted
Clague et al., 2017	Cross-sectional	Primary Care Clinical Informatics Unit (electronic database), University of Aberdeen, United Kingdom (2007)	**Dementia** - n: 10,528 - Age: 80-89 years (mode) - Sex: 29.4% male - Number of drugs: 5-9 (mode) **No dementia** - n: 280,641 - Age: 65-74 years (mode) - Sex: 43.3% male - Number of drugs: 5–9 (mode)	- Defined as 5–9 active repeated prescriptions - Excessive polypharmacy was defined as 9 or more active repeated prescriptions	- As defined by Read Code - Alzheimer's disease, vascular dementia, Lewy Body dementia, dementia associated with other conditions such as Parkinson's Disease and unspecified dementia	- Age - Sex - Comorbidities e.g. number of physical conditions
Lai et al., 2012	Case-control	Taiwan National Health Insurance Database, Taiwan (1996–2008)	**Case (dementia)** - n: 7,135 - Age: 78.92 ± 6.84 years (mean ± SD) - Sex: 49.4% male - Number of drugs: 2-4 (mode) **Control (no dementia)** - n: 28,540 - Age: 76.46 ± 5.72 years (mean ± SD) - Sex: 52.6% male - Number of drugs: 2–4 (mode)	- Defined as average daily use of 5 or more prescribed drugs	- As defined by International Classification of Diseases 9th Revision Clinical Modification (ICD-9 290.0, 290.1,290.2, 290.3, 290.4,294.1 and 331.0) - Age, - Sex - Number of medications - Comorbidities e.g. obesity, diabetes, hypertension, hyperlipidemia, cerebrovascular disease and chronic kidney disease	
Park et al., 2017	Nested case-control	The National Health Insurance Service-National Sample Cohort (NHIS-NSC) database, South Korea (2002)	- Community based **Case (dementia)** - n: 5,562 - Age: 73.3 ± 6.9 years (mean ± SD) - Sex: 28.2% male - Number of drugs: 2.54 ± 2.87 (mean ± SD **Control (no dementia)** - n: 5,562 - Age: 73.3 ± 6.9 years (mean ± SD) - Sex: 28.2% male - Number of drugs: 1.75 ± 2.39 (mean ± SD)	- Defined as average daily use of 5–9 prescribed drugs -Excessive polypharmacy was defined as 10 or more active repeated prescriptions	- As defined by ICD-10 Clinical Modification F00 (dementia in Alzheimer's disease), F01 (vascular dementia), F02 (dementia in other diseases classified elsewhere), F03 (unspecified dementia), F051 (delirium superimposed on dementia), G30 (Alzheimer's disease), and G311 (senile degeneration of the brain, not elsewhere classified)	- Comorbidities e.g. hypertension, peripheral or cerebrovascular disease, congestive heart failure, hemiplegia, diabetes, depression, all other mental disorders, chronic obstructive pulmonary disease, peptic ulcer disease, and chronic liver disease
Tjia et al., 2010	Prospective cohort	Nursing-homes in Boston as part of the Choices, Attitudes, and Strategies for Care in Advanced Dementia at the End-of-Life (CASCADE) study, United States (2003–2009)	- Community based - n: 1381 - Age: 84.9 ± 7.5 years (mean ± SD) - Sex: 12.5% male - Number of drugs: 5.9 ± 3.0 (mean ± SD)	- Defined as mean number of daily medication - Data from medication administration record	- Defined as dementia not due to Alzheimer's disease - CPS score = 5 or 6 and GDS score = 7 - Data from residents' medical records, a brief mental status examination, and interviews of nurses and health care proxies	- Clustering at the resident level
Vetrano et al., 2013	Cross-sectional	Nursing homes in 8 countries (Czech Republic, England, Finland, France, Germany, Italy, the Netherlands and Israel) as part of the Services and Health for Elderly in Long-Term Care (SHELTER) project (2009–2011)	- Institution based No polypharmacy (<5 drugs) - n: 69 - Age: 84.2 ± 9.7 years (mean ± SD) - Sex: 22.4% male - Number of drugs: no data Polypharmacy (5-9 drugs) - n: 735 - Age: 84.3 ± 8.5 years (mean ± SD) - Sex: 24.5% male - Number of drugs: no data Excessive polypharmacy (≥ 10 drugs) - n: 245 - Age: 84.0 ± 9.0 years (mean ± SD) - Sex: 31.0% male - Number of drugs: no data	- Defined as concurrent use of 5–9 drugs - Excessive Polypharmacy: concurrent use of ≥ 10 drugs - Data from physician order sheets and medication administration record	- Cognitive Performance Scale score = 4–6 - Data from International Resident Assessment Instrument (InterRAI) for longterm care facilities (InterRAI LTCF), structured interview, medical and nursing records	- Age - Sex - Comorbidities e.g. gastrointestinal symptoms, pain, dyspnea and specific diseases including ischemic heart disease, diabetes mellitus and Parkinson's disease
Voukelatou, Vrettos et al,, 2016	Cannot determine	General Oncological Hospital of Kifissia, Greece	- n: 276 - Age: 80.39 ± 8.02 years (mean ± SD)	- Defined as use of ≥ 5 drugs - Data from medical record		- Comorbidities e.g. arterial hypertension, coronary artery disease, heart failure,

(*continued*)

Table 1. Continued.

Author	Study design	Location and year of study	Demographics	Polypharmacy (exposure)	Dementia (outcomes)	Confounder adjusted
			- Sex: 49.6% male - Number of drugs: no data		- No definition - Data from medical records and medical history	atrial fibrillation, diabetes mellitus, COPD
Wawruch et al., 2008	Retrospective cohort	Department of Internal Medicine, Povazska Bystrica, Slovakia (2003–2005)	Hospital based - n: 600 - Age: 76.6 ± 6.5 years (mean ± SD) - Sex: 41.5% male - Number of drugs: 6.0 ± 2.3 (mean ± SD)	- Defined as concurrent use of ≥ 6 drugs - Data from medical records	- As defined by ICD-10 - Data from medical records	- Comorbidities e.g. diabetes mellitus, heart failure, arterial hypertension, cerebrovascular disease - Living alone
Weintraub et al., 2008	Cross-sectional	National Alzheimer's Coordinating Center Uniform Data Set, United States (2005–2007)	- Community based - n: 2,665 - Age: 77.1 ± 7.0 years (mean ± SD) - Sex: 41.0% male - Number of drugs: 4.5 ± 2.6	- Defined as using of ≥ 9 drugs	- Defined as CDR = 3	- Age - Sex - Comorbidities e.g. neuropsychiatric symptoms, hypertension, hypercholesterolemia, incontinence, cardiovascular disease, thyroid diseases, diabetes - Socio-demographic characteristics e.g. race, educational level, marital status, living arrangement

SS-IQCODE: Shorten Spanish version of the *Informant Questionnaire on Cognitive Decline in the Elderly*
CDR: Clinical Dementia Rating
CPS score: Cognitive Performance Scale score
GDS score: Global Deterioration Scale score

were independently extracted by the first and second authors. Disagreement was resolved by consensus. In case of insufficient information provided in the publications, the first author contacted the corresponding authors to retrieve the essential information.

Assessment of study quality

Study quality was independently evaluated by the first and second authors using the Newcastle-Ottawa Quality Assessment scale (GA Wells et al.). Disagreement was also resolved by consultation and consensus. The scale was used because it is valid, reliable and easy to use (Stang, 2010). For cross-sectional studies, a modified version of the Newcastle-Ottawa scale was used (Herzog et al., 2013). The comparability item in the assessment scale was evaluated using the control for age and neuropsychiatric comorbidities.

Statistical methods

Random effects models with inverse variance (IV) weighting were used in Review Manager (RevMan 5.3, The Nordic Cochrane Center, Copenhagen, Denmark). The heterogeneity of the underlying population was assessed using the Q-statistic and I^2 statistic (Woolf, 1955). For interpretation, I^2 values less than 30% were considered to be of negligible heterogeneity while I^2 values greater than 60% were considered to be heterogeneous (Higgins & Thompson, 2002). Publication bias was assessed by visually evaluating a funnel plot.

Results

Study characteristics

The systematic literature search retrieved 1452 non-redundant manuscripts. Two studies were found by reviewing reference lists (del Ser et al., 2005; Weintraub, Mercaldo, Harris, & Lau, 2008). According to the inclusion and exclusion criteria, 8 studies were selected, including 1 prospective cohort study (Tjia et al., 2010), 1 retrospective cohort study (Wawruch et al., 2008), 2 case-control studies (Lai et al., 2012; Park, Park, Song, Sohn, & Kwon, 2017), 3 cross-sectional studies (Clague, Mercer, McLean, Reynish, & Guthrie, 2017; Vetrano et al., 2013; Weintraub et al., 2008) and one study without the information for the study design (Voukelatou, Vrettos et al., 2016) (Figure 1). Some studies defined dementia according to the International Classification of Diseases, 9th revision (ICD-9) (Lai et al., 2012) or ICD-10 (Park et al., 2017; Wawruch et al., 2008). Dementia was also defined using the clinical scores e.g. Cognitive Performance Scale (Tjia et al., 2010; Vetrano et al., 2013) or the Clinical Dementia rating (Weintraub et al., 2008). A description of included studies is provided in Table 1, and the Newcastle-Ottawa assessment of study quality is summarized in Table 2. According to the Newcastle-Ottawa Quality Assessment, most of the studies were classified as high quality (Clague et al., 2017; Lai et al., 2012; Park et al., 2017; Vetrano et al., 2013; Weintraub et al., 2008), a few studies had lower quality (Tjia et al., 2010; Wawruch et al., 2008) and one study could not be

Table 2. Risk of bias assessment by Newcastle-Ottawa Assessment scale.

Case control studies									
	Selection (1 star for each)				Comparability of cases and controls (up to 2 stars)	Exposure (1 star for each)			
Author, year	Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of exposure	Ascertainment method	Non-responserate	Total */9
Lai et al., 2012	*	*	*	*	*	*	*	*	8
Park et al., 2017	*	*	*	*	*	*	*	*	8
Cohort studies									
	Selection (1 star for each)				Exposure (1 star for each)				
Author, year	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at the beginning	Comparability of cohorts (up to 2 stars)	Assessment of outcome	Follow-up duration	Adequacy of follow up	Total */9
Wawruch et al., 2008	*	*	*	-	-	*	-	-	4
Tjia et al., 2010	*	*	*	-	-	*	-	*	5
Cross-sectional studies									
	Selection (1 star for each)				Exposure (1 star for each)				
Author, year	Representativeness of the sample	Sample size	Ascertainment of exposure (up to 2 stars)	-	Comparability of cohorts (up to 2 stars)	Assessment of outcome (up to 2 stars)	Non-respondents	Statistical test	Total */10
Weintraub et al., 2008	*	*	**	-	**	**	*	*	10
Vetrano et al., 2013	*	*	**	-	**	**	-	*	9
Clague et al., 2017	*	*	**	-	*	**	-	*	8

-,*, and, ** mean 0,1 and 2 points for the assessment scale, respectively.

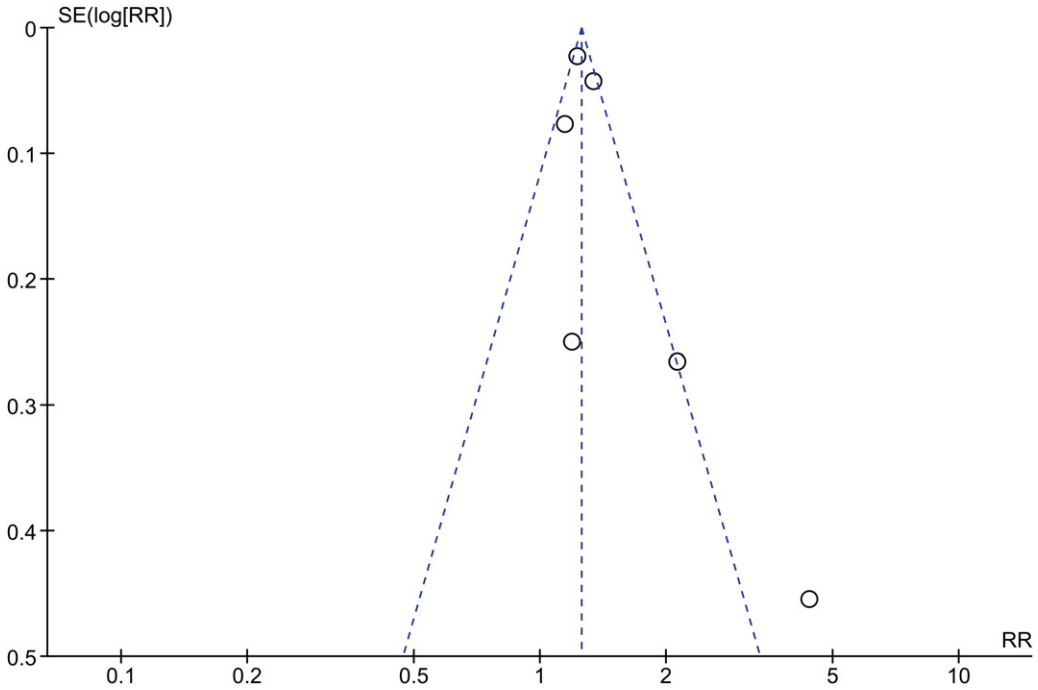

Figure 2. Funnel plot of adjusted association between polypharmacy and dementia. OR, odds ratio; SE, standard error.

assessed for study quality (Voukelatou, Vrettos et al., 2016) (Table 2).

A funnel plot of the adjusted association between polypharmacy and dementia was used to assess publication bias (Figure 2). Adjusted risk ratios were used to create the funnel plot because they tend to be closer to the null than their unadjusted counterparts and demonstrate less publication bias. The funnel plot showed the potential of publication bias since the standard error of log risk ratios was distributed heavily at the top, indicating that smaller studies might have not been published. Because of the small number of included publications, further tests for funnel plot asymmetry were not performed.

Descriptive review of included studies

Polypharmacy was prevalent in the elderly as it was observed in more than 50% of the patients (Vetrano et al., 2013; Wawruch et al., 2008). Most studies indicated a proportional increase in the risk of dementia with an increase in the number of medications (Lai et al., 2012; Park et al., 2017; Vetrano et al., 2013; Wawruch et al., 2008), and other studies reported that demented people received more than the average number of medications (Clague et al., 2017; Tjia et al., 2010). An increase in the number of medications has been associated with several other factors including older age (Tjia et al., 2010); comorbidities (acute illness, cardiovascular disease (such as hypertension, heart failure),

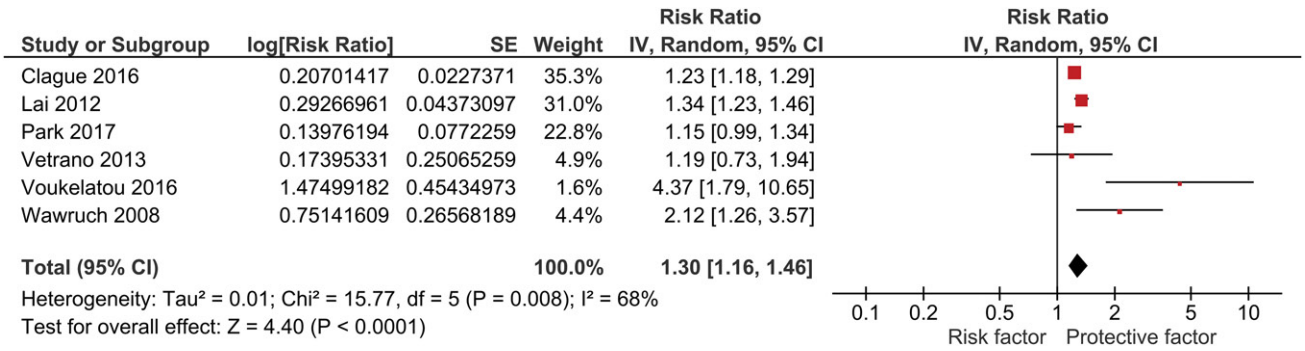

Figure 3. Forest plot of the association between polypharmacy and dementia. df, degree of freedom; IV, inverse variance; SE, standard error.

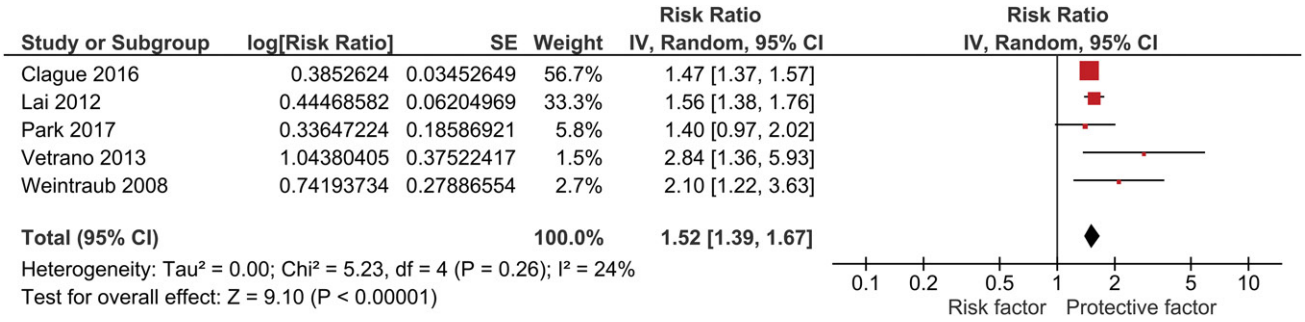

Figure 4. Forest plot of the association between excessive polypharmacy and dementia. df, degree of freedom; IV, inverse variance; SE, standard error.

cerebrovascular disease, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, depression, diabetes, gastrointestinal symptoms (such as peptic ulcer disease), hemiplegia, mental disorders and pain) (Lai et al., 2012; Park et al., 2017; Tjia et al., 2010; Vetrano et al., 2013; Wawruch et al., 2008); inappropriate use of medications (anticholinergics, H2-receptor antagonists (Park et al., 2017); recent hospitalization (Vetrano et al., 2013; Wawruch et al., 2008) and living alone (Wawruch et al., 2008). A lower prevalence of polypharmacy was observed with the presence of a geriatrician on the premises (Vetrano et al., 2013). From these included studies, we can conclude that polypharmacy was associated with dementia and other factors including age, comorbidities, specific symptoms, functional status and medical staff. Most studies suggested the need to tailor the number of medications to reduce polypharmacy (Voukelatou, Vrettos et al., 2016; Park et al., 2017; Tjia et al., 2010; Wawruch et al., 2008).

Concurrent drug use and risk of dementia

There were 7 studies that reported the association between polypharmacy and dementia. However, one study (Tjia et al., 2010) was not included in the meta-analysis because the reported risk ratio was based on a discrete definition of polypharmacy. The other studies defined polypharmacy as the concurrent use of 5-9 medications (Clague et al., 2017; Lai et al., 2012; Park et al., 2017; Vetrano et al., 2013), of more than 5 medications (P. Voukelatou, 2016) or of more than 6 medications (Wawruch et al., 2008). Tjia et al reported that an increase in one daily medication resulted in 24% increase in the risk of dementia (adjusted risk ratio (aRR) = 1.24 (95% CI: 1.06-1.46)). This meta-analysis found that polypharmacy increased the risk of dementia by 30% (aRR = 1.30 (95% CI: 1.16-1.46), p < 0.0001) (Figure 3). The result was heterogenous ($I^2 = 68\%$, $p = 0.008$) which may have been a result of the variation in the definition of polypharmacy in each study.

Excessive polypharmacy was also associated with an increase in the risk of dementia. When studies that defined excessive polypharmacy as the concurrent use of more than 9 or 10 medications (Clague et al., 2017; Lai et al., 2012; Park et al., 2017; Vetrano et al., 2013; Weintraub et al., 2008) were meta-analyzed, excessive polypharmacy was positively associated with dementia (aRR = 1.52 (95% CI: 1.39-1.67), p < 0.0001) (Figure 4). The heterogeneity in this analysis was negligible ($I^2 = 24\%$, $p = 0.26$). When the study that defined excessive polypharmacy as the concurrent use of more than 9 medications was excluded (Weintraub et al., 2008), the association between excessive polypharmacy and dementia did not change (aRR = 1.51 (95% CI: 1.39-1.64), p < 0.0001). However, the heterogeneity decreased ($I^2 = 20\%$, $p = 0.29$), demonstrating the importance of the definition of excessive polypharmacy on the heterogeneity of the studies.

Discussion

Polypharmacy, the concurrent use of multiple medications by an individual, has been found to be associated with several negative health outcomes. In this analysis, dementia was another negative health status that was associated with polypharmacy. Additionally, excessive polypharmacy which is the concurrent use of 10 or more medications by a patient, was also associated with dementia. The increase in the categorical threshold from 5 or more, to 10 or more, led to an increase in the risk of dementia from 30% to 52%, showing a dose- dependent relationship between the threshold value of polypharmacy and dementia. This finding agreed with our previous study which found that the mortality risk increased in a dose-dependent pattern when the threshold values for the number of medications

defining polypharmacy increased (Leelakanok et al., 2017). However, an attempt to classify included studies into categories using the number of medications exceeding a specified threshold as in our previous study was not made because of the small number of included studies.

The assessment of study quality by the Newcastle-Ottawa Quality Assessment Scale indicated that most of the included studies were of moderate to high quality, which implied minimal selection bias and comparable cases and controls. Nonetheless, other biases may have affected the association between polypharmacy and the risk of dementia. For example, several studies failed to adjust for age (Voukelatou, Vrettos et al., 2016; Park et al., 2017; Wawruch et al., 2008) and neurological co-morbidities (Clague et al., 2017; Voukelatou, Vrettos et al., 2016) which are the most important factors that cause dementia (Emre, 2009). Numerous comorbidities that are known to be associated with dementia e.g. congestive heart failure, cerebrovascular disease, anemia, cardiac arrhythmia, chronic skin ulcers, osteoporosis, thyroid disease, retinal disorders, prostatic hypertrophy, insomnia and anxiety and neurosis (Poblador-Plou et al., 2014), were also not adjusted for in most studies. Using the Charlson Comorbidity Index and Elixhauser Comorbidity Measure which are associated with mortality and short term clinical outcomes, respectively; (Molto & Dougados, 2014) as summarizing indices for comorbidities may be helpful in reducing the number of adjusting variables in the model. Interestingly, none of the included studies adjusted for types of medications. As mentioned earlier in the introduction, some medications demonstrate a positive association with dementia, while others show a negative association with dementia. Adjusting for the types of medications would help reduce the effect of this confounder. Further, the association between polypharmacy and dementia could have been affected by unmeasured confounders such as education (Sharp & Gatz, 2011), recent hospitalization, nutritional status (Arnljots, Thorn, Elm, Moore, & Sundvall, 2017; Emre, 2009), exposure to metal ions (Emre, 2009), genetics (Jorm et al., 2007), estrogen effect (Rocca, Mielke, Vemuri, & Miller, 2013) and obesity (van der Flier & Scheltens, 2005) to name a few. Moreover, most of the cohort studies (Wawruch et al., 2008) and cross-sectional studies (Clague et al., 2017; Vetrano et al., 2013) failed to report the follow-up duration and nonrespondents rate, respectively. Therefore, selection bias due to loss to follow-up is possible in those selected studies.

The quality of this meta-analysis was affected by the inclusion of two low quality studies. The small number of selected studies prevented subset analysis using only the high-quality studies. Most of the included studies discussed limitations in studying the association between polypharmacy and dementia. These included difficulties in detecting early onset dementia and recording dementia in general practice (Clague et al., 2017); diverse definitions of polypharmacy (number of medications or medication appropriateness) (Wawruch et al., 2008); confounding effect of medical inappropriateness when polypharmacy was considered as the number of medications (Lai et al., 2012) since there is an association between polypharmacy and potentially inappropriate medications (Alh- moud, Khalifa, & Bahi, 2015); and diverse definitions of medications (e.g. should topical medications be counted?) (Vetrano et al., 2013). These reports agree with our finding that included studies defined polypharmacy differently. Our results demonstrated that the variety of threshold for the definition of excessive polypharmacy may have influenced the homogeneity of the studies.

Another limitation of our meta-analysis is that many other studies could have contributed to this meta-analysis but were excluded because either the reported exposure or outcome, were not of interest. For instance, some studies defined polypharmacy as antipsychotic polypharmacy (Wu, Lai, & Chang, 2013) or as inappropriate drug use (Alhmoud et al., 2015). Others defined the outcome as cognitive impairment (del Ser et al., 2005; Fratiglioni, 2011; Gnjidic et al., 2012; Trombim et al., 2016), or reported confusion and dementia as a composite outcome (Kalisch Ellett, Pratt, Ramsay, Barratt, & Rough- ead, 2014). Results from previously published reports agree with the result from this systematic review and meta-analysis. For instance, antipsychotic polypharmacy was significantly more common in patients with dementia (OR = 3.49 (95% CI: 1.29–9.39), $p < 0.05$) (Wu et al., 2015). In addition, patients taking two or more anticholinergic medications were at a significantly higher risk of hospitalization for confusion or dementia (Kalisch Ellett et al., 2014). However, the association between number of medications and cognitive impairment was inconclusive. On one hand, no association between increasing number of medications and cognitive impairment (OR 1.02 (95% CI: 0.96–1.09), $p < 0.05$) (Gnjidic et al., 2012), or between polypharmacy and clinical dementia rating ($p = 0.68$) (Trombim et al., 2016) was found. On the other hand, number of prescribed drugs was significantly associated with cognitive deterioration measured as Short Portable Mental Status Questionnaire (SPMQ) (OR = 1.34 (95% CI: 1.05–1.72), $p < 0.05$) (del Ser et al., 2005) and amnestic mild cognitive impairment (OR 3.1 (95% CI: 1.2–8.0), $p < 0.05$) (Fratiglioni, 2011). With the diverse definitions of cognitive impairment in these studies, it is difficult to conclude the association between polypharmacy and cognitive impairment. Since cognitive impairment is only one of the components in the diagnosis of dementia (Brown, 2015), it is also possible that polypharmacy was associated with cognitive impairment but not with dementia.

This systematic review and meta-analysis was performed in the elderly population with comorbidities mimicking the patients with polypharmacy in clinical situations. Polypharmacy is most common in the elderly, with nursing homes residents taking the highest number of drugs, and this has been a growing concern over the last few decades (Maher, Hanlon, & Hajjar, 2014). Therefore, the result from this meta-analysis was generalizable and raised the concern about the negative impact of polypharmacy on a patient's cognitive, emotional and conative functions. However, this interpretation must be contemplated with caution. The conclusion that polypharmacy causes dementia cannot be drawn because of the effect of known confounders that were not adjusted for in each included study. Polypharmacy increases the risk of inappropriate drug use (Alhmoud et al., 2015; Bradley et al., 2014; Hudhra et al., 2016; Parsons, 2017), adverse drug events (Alha- wassi, Krass, Bajorek, & Pont, 2014; Fulton & Allen, 2005; Maher et

al., 2014), drug-drug interactions (Alomar, 2014; Sharifi, Hasanloei, & Mahmoudi, 2014) and reduced medication adherence (Murray & Kroenke, 2001) which can affect the central nervous system (Borchelt, 1995; Malek & Grosset, 2015; Morrone, Schroeter, Petitembert, Faggiani, & De Carli, 2009; Onda et al., 2015; Sharifi et al., 2014; Weiner, Hanlon, & Stu- denski, 1998). One of the included studies stated that polypharmacy may increase the risk of dementia-related, potentially inappropriate medications. This may occur even when the potentially inappropriate medications were not identified (Parket al., 2017). However, polypharmacy can also be a result of patients with severe mental status requiring multiple medications for their treatment (Riccio, Solinas, Astara, & Mantovani, 2007; Sadowsky & Galvin, 2012).

Dementia is currently diagnosed based on clinical context without any biological markers (Galvin & Sadowsky, 2012). This meta-analysis supports the use of multidimensional diagnostic tools for dementia that included the number of medications as a component (Riccio et al., 2007), since polypharmacy is a strong predictor for dementia. To properly address the association between polypharmacy and dementia, a large, well-designed observational study that controls for all known confounders, especially comorbidities and type of medications, is required. Comorbidity indices can be used to summarize the effect of comorbidities. Although there is no universal index for summarizing the effect of drugs, the use of drug burden index may be helpful in measuring the cumulative effect of sedatives and anticholinergics (Kouladjian, Gnjidic, Chen, Mangoni, & Hilmer, 2014). The effect of other known confounding medications such as estrogen, proton pump inhibitors, metformin, HMG-CoA reductase inhibitors and nonsteroidal anti-inflammatory drugs must also be justified. Proving the effect of deprescribing, which is a planned and supervised process of dose reduction or stopping of medication to limit harm to patients and to restrict polypharmacy to its truly appropriate need, is another approach to study the association between polypharmacy and dementia.

Geolocation information

None

Acknowledgement

We thank Sandra Weintraub, Nathaniel Mercaldo and Denys T. Lau for providing detailed information from their publications.

Disclosure statement

Nattawut Leelakanok and Ronilda R. D' Cunha report no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ORCID

Nattawut Leelakanok http://orcid.org/0000-0003-3533-4775

References

Alhawassi, T. M., Krass, I., Bajorek, B. V., & Pont, L. G. (2014). A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clinical Interventions in Aging, 9, 2079–2086. doi:10.2147/CIA.S71178

Alhmoud, E., Khalifa, S., & Bahi, A. A. (2015). Prevalence and predictors of potentially inappropriate medications among home care elderly patients in Qatar. International Journal of Clinical Pharmacy, 37(5), 815–821. doi:10.1007/s11096-015-0125-0

Alomar, M. J. (2014). Factors affecting the development of adverse drug reactions (Review article). Saudi Pharmaceutical Journal, 22(2), 83–94. doi:10.1016/j.jsps.2013.02.003

Andersen, F., Viitanen, M., Halvorsen, D. S., Straume, B., & Engstad, T. A. (2011). Co-morbidity and drug treatment in Alzheimer's disease. A cross sectional study of participants in the Dementia Study in Northern Norway. BMC Geriatrics, 11(1), 58. doi:10.1186/1471-2318-11-58

Arnljots, R., Thorn, J., Elm, M., Moore, M., & Sundvall, P. D. (2017). Vitamin D deficiency was common among nursing home residents and associated with dementia: A cross sectional study of 545 Swedish nursing home residents. BMC Geriatrics, 17(1), 229. doi:10.1186/s12877-017-0622-1

Borchelt, M. (1995). [Potential side-effects and interactions in multiple medication in elderly patients: Methodology and results of the Berlin Study of Aging]. Zeitschrift Fur Gerontologie Und Geriatrie, 28(6), 420–428.

Bradley, M. C., Motterlini, N., Padmanabhan, S., Cahir, C., Williams, T., Fahey, T., & Hughes, C. M. (2014). Potentially inappropriate prescribing among older people in the United Kingdom. BMC Geriatrics, 14(1), 72. doi:10.1186/1471-2318-14-72

Brodaty, H., & Donkin, M. (2009). Family caregivers of people with dementia. Dialogues in Clinical Neuroscience, 11(2), 217–228.

Brown, J. (2015). The use and misuse of short cognitive tests in the diagnosis of dementia. Journal of Neurology, Neurosurgery & Psychiatry, 86 (6), 680–685. doi:10.1136/jnnp-2014-309086

Chen, J. H., Lin, K. P., & Chen, Y. C. (2009). Risk factors for dementia. Journal of the Formosan Medical Association, 108(10), 754–764. doi:10.1016/s0929-6646(09)60402-2

Chertkow, H., Feldman, H. H., Jacova, C., & Massoud, F. (2013). Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: Consensus from the Canadian conference on diagnosis of dementia. Alzheimer's Research & Therapy, 5(Suppl 1), S2.doi:10.1186/alzrt198

Clague, F., Mercer, S. W., McLean, G., Reynish, E., & Guthrie, B. (2017). Comorbidity and polypharmacy in people with dementia: Insights from a large, population-based cross-sectional analysis of primary care data. Age and Ageing, 46(1), 33–39. doi:10.1093/ageing/afw176

Cool, C., Cestac, P., Laborde, C., Lebaudy, C., Rouch, L., Lepage, B., … Lapeyre-Mestre, M. (2014). Potentially inappropriate drug prescribing and associated factors in nursing homes. Journal of the American Medical Directors Association, 15(11), 850.e851–859. doi:10.1016/j.jamda.2014.08.003

del Ser, T., Barba, R., Morin, M. M., Domingo, J., Cemillan, C., Pondal, M., & Vivancos, J. (2005). Evolution of cognitive impairment after stroke and risk factors for delayed progression. Stroke; A Journal of Cerebral Circulation, 36(12), 2670–2675. doi:10.1161/01.str.0000189626.71033.35

Emre, M. (2009). Classification and diagnosis of dementia: A mechanism- based approach. European Journal of Neurology, 16(2), 168–173. doi:10.1111/j.1468-1331.2008.02379.x

Fratiglioni, L. (2011). MCI: Occurrence, risk factors, progression; evidence from the Kungsholmen project. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 7(4), S495. doi:10.1016/j.jalz.2011.05.2384

Fulton, M. M., & Allen, E. R. (2005). Polypharmacy in the elderly: A literature review. Journal of the American Academy of Nurse Practitioners, 17(4), 123–132. doi:10.111/j.1041-2972.2005.0020.x

Galvin, J. E., & Sadowsky, C. H. (2012). Practical guidelines for the recognition and diagnosis of dementia. Journal of the American Board of Family Medicine, 25(3), 367–382. doi:10.3122/jabfm.2012.03.100181

Gnjidic, D., Hilmer, S. N., Blyth, F. M., Naganathan, V., Waite, L., Seibel, M. J., … Le Couteur, D. G. (2012). Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. Journal of Clinical Epidemiology, 65(9), 989–995. doi:10.1016/j.jclinepi.2012.02.018

Gomm, W., von Holt, K., Thome, F., Broich, K., Maier, W., Fink, A., … Hae- nisch, B. (2016). Association of proton pump inhibitors with risk of dementia: A Pharmacoepidemiological claims data analysis. JAMA Neurology, 73(4), 410–416. doi:10.1001/jamaneurol.2015.4791

Gomm, W., von Holt, K., Thome, F., Broich, K., Maier, W., Weckbecker, K., … Haenisch, B. (2016). Regular benzodiazepine and Z-Substance use and risk of dementia: An analysis of German claims data. Journal of Alz- heimers Disease, 54(2), 801–808. doi:10.3233/jad-151006

Green, A. R., Segal, J., Tian, J., Oh, E., Roth, D. L., Hilson, L., … Boyd, C. M. (2017). Use of bladder Antimuscarinics in older adults with impaired cognition. Journal of the American Geriatrics Society, 65(2), 390–394. doi:10.1111/jgs.14498

Gupta, M., Singh, R., Singh, K., & Lehl, S. S. (2013). Reversible dementia and gait disturbance as a result of polypharmacy. BMJ Case Reports, 2013, 1–2. doi:10.1136/bcr-2013-008932

Haenisch, B., von Holt, K., Wiese, B., Prokein, J., Lange, C., Ernst, A., … Scherer, M. (2015). Risk of dementia in elderly patients with the use of proton pump inhibitors. European Archives of Psychiatry and Clinical Neuroscience, 265(5), 419–428. doi:10.1007/s00406-014-0554-0

Herzog, R., Alvarez-Pasquin, M. J., Diaz, C., Del Barrio, J. L., Estrada, J. M., & Gil, A. (2013). Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health [Electronic Resource], 13, 154. doi:10.1186/1471-2458-13-154

Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. Statistics in Medicine, 21(11), 1539–1558. doi:10.1002/sim.1186

Hudhra, K., Garcia-Caballos, M., Casado-Fernandez, E., Jucja, B., Shabani, D., & Bueno-Cavanillas, A. (2016). Polypharmacy and potentially inappropriate prescriptions identified by Beers and STOPP criteria in co-morbid older patients at hospital discharge. Journal of Evaluation in Clinical Practice, 22(2), 189–193. doi:10.1111/jep.12452

Hulse, G. K., Lautenschlager, N. T., Tait, R. J., & Almeida, O. P. (2005). Dementia associated with alcohol and other drug use. International Psychogeriatrics, 17(Suppl 1), S109–S127.

Jorm, A. F., Mather, K. A., Butterworth, P., Anstey, K. J., Christensen, H., & Easteal, S. (2007). APOE genotype and cognitive functioning in a large age-stratified population sample. Neuropsychology, 21(1), 1–8. doi:10.1037/0894-4105.21.1.1

Kalisch Ellett, L. M., Pratt, N. L., Ramsay, E. N., Barratt, J. D., & Roughead, E. E. (2014). Multiple anticholinergic medication use and risk of hospital admission for confusion or dementia. Journal of the American Geriatrics Society, 62(10), 1916–1922. doi:10.1111/jgs.13054

Kose, E., Maruyama, R., Okazoe, S., & Hayashi, H. (2016). Impact of Polypharmacy on the rehabilitation outcome of Japanese stroke patients in the convalescent rehabilitation ward. Journal of Aging Research, 2016, 8. doi:10.1155/2016/7957825

Kouladjian, L., Gnjidic, D., Chen, T. F., Mangoni, A. A., & Hilmer, S. N. (2014). Drug burden index in older adults: Theoretical and practical issues. Clinical Interventions in Aging, 9, 1503–1515. doi:10.2147/CIA.S66660

Lai, S. W., Lin, C. H., Liao, K. F., Su, L. T., Sung, F. C., & Lin, C. C. (2012). Association between polypharmacy and dementia in older people: A population-based case-control study in Taiwan. Geriatrics & Gerontology International, 12(3), 491–498. doi:10.1111/j.1447-0594.2011.00800.x

Lau, D. T., Mercaldo, N. D., Harris, A. T., Trittschuh, E., Shega, J., & Wein- traub, S. (2010). Polypharmacy and potentially inappropriate medication use among community-dwelling elders with dementia. Alzheimer Disease and Associated Disorders, 24(1), 56–63. doi:10.1097/WAD.0b013e31819d6ec9

Lau, D. T., Mercaldo, N. D., Shega, J. W., Rademaker, A., & Weintraub, S. (2011). Functional decline associated with polypharmacy and potentially inappropriate medications in community-dwelling older adults with dementia. American Journal of Alzheimers Disease and Other Dementias, 26(8), 606–615. doi:10.1177/1533317511432734

Leelakanok, N., Holcombe, A. L., Lund, B. C., Gu, X., & Schweizer, M. L. (2017). Association between polypharmacy and death: A systematic review and meta-analysis. Journal of the American Pharmaceutical Association, 57(6), 729–738.e710. doi:10.1016/j.japh.2017.06.002

Maher, R. L., Hanlon, J. T., & Hajjar, E. R. (2014). Clinical consequences of polypharmacy in elderly. Expert Opinion on Drug Safety, 13(1), 1–11. doi:10.1517/14740338.2013.827660

Malek, N., & Grosset, D. G. (2015). Medication adherence in patients with Parkinson's disease. CNS Drugs, 29(1), 47–53. doi:10.1007/s40263-014-0220-0

Mate, K. E., Kerr, K. P., Pond, D., Williams, E. J., Marley, J., Disler, P., … Magin, P. J. (2015). Impact of multiple low-level anticholinergic medications on anticholinergic load of community-dwelling elderly with and without dementia. Drugs & Aging, 32(2), 159–167. doi:10.1007/s40266-014-0230-0

McCracken, R., McCormack, J., McGregor, M. J., Wong, S. T., & Garrison, S. (2017). Associations between polypharmacy and treatment intensity for hypertension and diabetes: A cross-sectional study of nursing home patients in British Columbia, Canada. BMJ Open, 7(8), 1–6. doi:10.1136/bmjopen-2017-017430

McCullagh, C. D., Craig, D., McIlroy, S. P., & Passmore, A. P. (2001). Risk factors for dementia. Advances in Psychiatric Treatment, 7(1), 24–31. doi:10.1192/apt.7.1.24

Molto, A., & Dougados, M. (2014). Comorbidity indices. Clinical and Experimental Rheumatology, 32(5 Suppl 85), S–131–134.

Monastero, R., Palmer, K., Qiu, C., Winblad, B., & Fratiglioni, L. (2007). Heterogeneity in risk factors for cognitive impairment, no dementia: Population-based longitudinal study from the Kungsholmen Project. American Journal of Geriatric Psychiatry, 15(1), 60–69. doi:10.1097/01.jgp.0000229667.98607.34

Morrone, F. B., Schroeter, G., Petitembert, A. P., Faggiani, F. T., & De Carli, G. A. (2009). Potential interactions of central nervous system drugs used in the elderly population. Brazilian Journal of Pharmaceutical Sciences, 45, 227–234.

Murray, M. D., & Kroenke, K. (2001). Polypharmacy and medication adherence: Small steps on a long road. Journal of General Internal Medicine, 16(2), 137–139. doi:10.1111/j.1525-1497.2001.01229.x

Onda, M., Imai, H., Takada, Y., Fujii, S., Shono, T., & Nanaumi, Y. (2015). Identification and prevalence of adverse drug events caused by potentially inappropriate medication in homebound elderly patients: A retrospective study using a nationwide survey in Japan. BMJ Open, 5 (8), e007581. doi:10.1136/bmjopen-2015-007581

Orkaby, A. R., Cho, K., Cormack, J., Gagnon, D. R., & Driver, J. A. (2017). Metformin vs sulfonylurea use and risk of dementia in US veterans aged >/=65 years with diabetes. Neurology, 89(18), 1877–1885. doi:10.1212/wnl.0000000000004586

Ostrom, J. R., Hammarlund, E. R., Christensen, D. B., Plein, J. B., & Kethley, A. J. (1985). Medication usage in an elderly population. Medical Care, 23 (2), 157–164.

Park, H.-Y., Park, J.-W., Song, H. J., Sohn, H. S., & Kwon, J.-W. (2017). The association between polypharmacy and dementia: A nested case-control study based on a 12-Year longitudinal cohort database in South Korea. Plos One, 12(1), e0169463. doi:10.1371/journal.pone.0169463

Parsons, C. (2017). Polypharmacy and inappropriate medication use in patients with dementia: An underresearched problem. Therapeutic Advances in Drug Safety, 8(1), 31–46. doi:10.1177/2042098616670798

Poblador-Plou, B., Calderon-Larranaga, A., Marta-Moreno, J., Hancco-Saa- vedra, J., Sicras-Mainar, A., Soljak, M., & Prados-Torres, A. (2014). Comorbidity of dementia: A cross-sectional study of primary care older patients. BMC Psychiatry [Electronic Resource], 14, 84–84. doi:10.1186/1471-244X-14-84

Rattagan, M. L., Lisei, D., Rojas, G. J., Persi, G. G., Parisi, V. L., Lopez Vicchi, M., … Gatto, E. M. (2016). [Rational use of psychotropic medications and sedative load in older adults with and without dementia]. Vertex (Buenos Aires, Argentina), XXVII(129), 332–338.

Riccio, D., Solinas, A., Astara, G., & Mantovani, G. (2007). Comprehensive geriatric assessment in female elderly patients with Alzheimer disease and other types of dementia. Archives of Gerontology and Geriatrics, 44 (Suppl 1), 343–353. doi:10.1016/j.archger.2007.01.047

Rizzi, L., Rosset, I., & Roriz-Cruz, M. (2014). Global epidemiology of dementia: Alzheimer's and vascular types. BioMed Research International, 2014, 8. doi:10.1155/2014/908915

Rocca, W. A., Mielke, M. M., Vemuri, P., & Miller, V. M. (2014). Sex and gender differences in the causes of dementia: A narrative review. Maturi- tas, 79(2), 196–201. doi:10.1016/j.maturitas.2014.05.008

Sadowsky, C. H., & Galvin, J. E. (2012). Guidelines for the management of cognitive and behavioral problems in dementia. Journal of the American Board of Family Medicine, 25(3), 350–366. doi:10.3122/jabfm.2012.03.100183

Sarkar, U., Lyles, C., Steinman, M., Huang, E. S., Moffet, H. H., Whitmer, R. A., … Karter, A. J. (2017). Changes in medication use after dementia diagnosis in an observational cohort of individuals with diabetes mellitus. Journal of the American Geriatrics Society, 65(1), 77–82. doi:10.1111/jgs.14429

Schubert, C. C., Boustani, M., Callahan, C. M., Perkins, A. J., Carney, C. P., Fox, C., . Hendrie, H. C. (2006). Comorbidity profile of dementia patients in primary care: Are they sicker ? Journal of the American Geriatrics Society, 54(1), 104–109. doi:10.1111/j.1532-5415.2005.00543.x

Sharifi, H., Hasanloei, M. A., & Mahmoudi, J. (2014). Polypharmacy-induced drug-drug interactions; threats to patient safety. Drug Research (Stuttg), 64(12), 633–637. doi:10.1055/s-0033-1363965

Sharp, E. S., & Gatz, M. (2011). Relationship between education and dementia: An updated systematic review. Alzheimer Disease and Associated Disorders, 25(4), 289–304. doi:10.1097/WAD.0b013e318211c83c

Shumaker, S. A., Legault, C., Kuller, L., Rapp, S. R., Thal, L., Lane, D. S., … Coker, L. H. (2004). Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA, 291 (24), 2947–2958. doi:10.1001/jama.291.24.2947

Silay, K., Yalcin, A., Akinci, S., Gursoy, F. G., & Sener Dede, D. (2017). Charl- son Comorbidity Index, inappropriate medication use and cognitive impairment: Bermuda Triangle. Wiener Klinische Wochenschrift, 129 (21–22), 799–804. doi:10.1007/s00508-017-1253-4

Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European Journal of Epidemiology, 25(9), 603–605. doi:10.1007/s10654-010-9491-z

Starr, J. M., & Whalley, L. J. (1994). Drug-induced dementia. Incidence, management and prevention. Drug Safety, 11(5), 310–317.

Tjia, J., Rothman, M. R., Kiely, D. K., Shaffer, M. L., Holmes, H. M., Sachs, G. A., & Mitchell, S. L. (2010). Daily medication use in nursing home residents with advanced dementia. Journal of the American Geriatrics Society, 58(5), 880–888. doi:10.1111/j.1532-5415.2010.02819.x

Trombim, L. B., Fermino, B. L., Kruger, A. J., Vaz, F. N. C., Nascimento, L., Silva, W. C. F. N. d., … Bonini, J. S. (2016). Incidence of polypharmacy in Alzheimer's disease elderly patients from Guarapuava City (Parana, Brazil). African Journal of Pharmacy and Pharmacology, 10(17), 364369.

van der Flier, W. M., & Scheltens, P. (2005). Epidemiology and risk factors of dementia. Journal of Neurology, Neurosurgery, and Psychiatry, 76 (Suppl 5), v2–v7. doi:10.1136/jnnp.2005.082867

Vetrano, D. L., Tosato, M., Colloca, G., Topinkova, E., Fialova, D., Gindin, J., … Onder, G. (2013). Polypharmacy in nursing home residents with severe cognitive impairment: Results from the SHELTER Study. Alzheimer's Dementia, 9(5), 587–593. doi:10.1016/j.jalz.2012.09.009

Virot, P. (2017). 10 facts on dementia. Retrieved from http://origin.who.int/features/factfiles/dementia/en/

Voukelatou, P., Vrettos, I., Bitsikokou, A., Rapti, E., Sfendouraki, E., Ragkou, A., … Kalliakmanis, A. (2016). Diseases linked to polypharmacy and consequences of multiple drug use in consecutively admitted elderly patients at the time of admission. European Geriatric Medicine, 7S1, S29–S259.

Wawruch, M., Zikavska, M., Wsolova, L., Kuzelova, M., Tisonova, J., Gajdosik, J., . Kristova, V. (2008). Polypharmacy in elderly hospitalised patients in Slovakia. Pharmacy World & Science, 30(3), 235–242. doi:10.1007/s11096-007-9166-3

Weiner, D. K., Hanlon, J. T., & Studenski, S. A. (1998). Effects of central nervous system polypharmacy on falls liability in community-dwelling elderly. Gerontology, 44(4), 217–221.

Weintraub, S., Mercaldo, N., Harris, A. T., & Lau, D. T. (2008). P2-281: Polypharmacy among community-dwelling elderly patients with dementia: Analysis of the National Alzheimer's Coordinating Center uniform data set. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 4(4), T454. doi:10.1016/j.jalz.2008.05.1357

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tug- well, P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Retrieved from http://www. ohri.ca/programs/clinical_epidemiology/oxford.asp

Wimo, A., Jonsson, L., Bond, J., Prince, M., & Winblad, B. (2013). The worldwide economic impact of dementia 2010. Alzheimer's Dementia, 9(1), 1–11.e13. doi:10.1016/j.jalz.2012.11.006

Woolf, B. (1955). On estimating the relation between blood group and disease. Annals of Human Genetics, 19(4), 251–253.

Wu, Y. H., Lai, C. Y., & Chang, Y. S. (2015). Antipsychotic polypharmacy among elderly patients with schizophrenia and dementia during hospitalization at a Taiwanese psychiatric hospital. Psychogeriatrics, 15(1), 7–13. doi:10.1111/psyg.12067