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Review

Scoping review of the association of health literacy and numeracy with medication adherence among adults with Type 2 diabetes

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ABSTRACT

One of the pillars of diabetes management is the adherence of patients to their medication regimen. However, patients with Type 2 diabetes (T2DM) become non-adherent when they have a poor understanding of their regimen due to low health literacy and numeracy skills. This study comprehensively reviews research which estimated the association of health literacy and numeracy with medication adherence of adult, T2DM patients. Seventeen articles which involved 4,384 participants were included. Only six studies (35.3%) found a significant association between health literacy and adherence with two also having a significant link between numeracy and adherence. The quality of the included studies was evaluated using the adapted Newcastle-Ottawa Scale. In conclusion, the association among the variables studied remains unclear, but the results of the review highlight the importance of quantitatively exploring the impact of health literacy and numeracy along with the other patient-related characteristics that may affect medication adherence.

Key words: adherence, diabetes, health literacy, numeracy

1. Background

According to the International Diabetes Federation (IDF, 2019), there is an estimated 463 million adults who have diabetes mellitus (DM) worldwide. This number is projected to reach 700 million by 2045, with Type 2 Diabetes Mellitus (T2DM) increasing in most countries (IDF, 2019). Diabetes mellitus is characterized by chronic hyperglycemia which can lead to various macrovascular and microvascular complications if not managed (Fauci et al., 2008). As of 2019 (IDF), there have been 4.2 million deaths accounted for by diabetes.

The goals of medication therapy for diabetes include maintenance of the blood glucose levels at the target range and avoidance of any complications that can be precipitated by the disease (WHO, 2003). Studies showed that the majority of diabetic patients have difficulty adhering to their medication therapy and practicing self-care activities. Some of the factors identified that affect adherence are the quality of relationship and communication between a diabetic patient and the healthcare provider, complexity of dosing regimens, and adverse events associated with the medications (García-Pérez et al., 2013; WHO, 2003).

Medication adherence is defined as the process by which patients take the medications as prescribed by the healthcare provider. It encompasses all events starting from the time of prescribing until the end of the prescribing period (Vrijens et al., 2012). Medication adherence can be assessed with objective and subjective measures (Lam and Fresco, 2015; WHO, 2003). Several studies on medication adherence to diabetes medications revealed a wide variety on the prevalence of adherence. Most of the published studies have observed low prevalence of adherence among diabetic patients (Cramer, 2004; Krass et al., 2015). With pharmacological treatment as one of the pillars of diabetes management, poor medication adherence is proven to be associated with poor clinical outcomes such as inadequate glycemic control, increased occurrence of complications, and even increased mortality (Polonsky and Henry, 2016).

Most of the components of diabetes management rely on the involvement and the ability of patients to adhere, making health literacy an important factor that can influence the management of their disease. Health literacy is formally defined by the Institute of Medicine as the degree to which the users of health information and services can obtain, process, and understand these information and services for them to make appropriate health decisions (Nielsen-Bohlman et al., 2004). Health literacy has three domains, namely:

functional, communicative, and critical. Functional literacy is the basic level of health literacy that pertains to a patient's reading and writing skills. Communicative literacy is the advanced level of health literacy that pertains to a patient's ability to extract and apply information. Critical health literacy refers to a patient's ability to critically analyze and use information for a greater control over situations (Hejimans et al., 2015; Nutbeam, 2000). Another component of health literacy that should be considered is numeracy (IOM, 2004). Numeracy broadly refers to the ability of a person to understand and use numbers in their daily lives (Rothman et al., 2008). Diabetes-related numeracy specifically refers to the skills needed in the context of diabetes management which can include interpretation of blood glucose self-monitoring results, administration or intake of diabetes medicines in correct amounts, and following nutritional recommendations (Cavanaugh et al., 2008; Huizinga et al., 2008).

Poor health literacy has been linked with poor health outcomes among patients. Patients with poor health literacy delay or have difficulties accessing health services, have higher severity of disease upon diagnosis, or misuse medications which lead to increase hospitalizations, increased demand of care, higher healthcare costs, decreased preventive care, and higher risk of premature death (Berkman et al., 2011; Cavanaugh et al., 2008; Palumbo, 2017; Schillinger, 2020). Diabetic patients with low health literacy and numeracy are observed to have low diabetes knowledge and perceived self-efficacy. This leads to less participation in diabetes self-management and worse glycemic control (Cavanaugh et al., 2008; Schillinger, 2020). Also, patients with a poor understanding of their medications are more likely to be non-adherent because of their low ability and skills to follow their prescribed drug regimen. Provision of medication and health information will not ensure improved health outcomes for a patient who might have poor health literacy. This will make the provision of information futile if there is a disconnect between the level of information provided and health literacy of the recipient of information (Cavanaugh et al., 2008; Chen et al., 2013; Johnson et al., 2013; Tcakz, 2008).

With the numerous studies conducted to establish the effect of health literacy on medication adherence among diabetic patients, systematic reviews revealed conflicting results on its association ranging from no association to a direct positive association (Chima et al., 2020; Dahal and Hosseinzadeh, 2019; Loke et al., 2012). These existing reviews had varying inclusion and exclusion criteria such as no consideration of numeracy, geographic location, and diversity of patients considered that may have contributed to the inconclusive results of these reviews. The study shall address the limitations of existing reviews on the association of health literacy and medication adherence by not limiting the setting and population of studies to be included. Also, several relevant studies have been conducted since the publication of the available systematic reviews. Lastly, there are no scoping reviews that explored the association of both health literacy and numeracy with medication adherence to date. As such, this scoping review aims to examine the association of health literacy and numeracy with medication adherence of adult T2DM patients as reported in existing evidence.

2. Methodology

2.1. Search Strategy

An exhaustive literature search was conducted in 3 databases: MEDLINE via PubMed, Scopus, and CINAHL Complete. The search process was conducted by two authors (KG, MG) independently. For a comprehensive review, all articles published from inception of the databases until April 2021 were included in the evaluation. Searching through the reference list of relevant articles and available systematic reviews (Chima et al., 2020; Dahal and Hosseinzadeh, 2019; Loke et al., 2012) as well as grey literature through WorldCat was conducted. The targeted articles included the following keywords: diabetes, literacy, numeracy, adherence. The search string used in all three databases include: (diabetic OR diabetes OR diabet* OR "type 2 diabetes" OR "diabetes mellitus" OR T2DM) AND (literacy OR numeracy) AND (adherence OR "medication engagement") AND (association OR effect OR impact). The citations and abstracts of search results were exported to MS Excel.

2.2. Study Selection

Upon collection of all search results from the three databases and additional records identified through hand searching, duplicates were removed. The records were screened by evaluating their relevance to the objective of this review based on the title and abstracts. Excluded articles were not primary studies, not relevant to the population, intervention, or outcome. After screening, full-text articles were retrieved to evaluate its eligibility. These were independently reviewed by two authors (KG, MG) to determine their eligibility based on the selection criteria. Disagreements on the included studies were resolved through a discussion with the third author (IP).

Articles are classified as eligible based on the following criteria: (1) original article, (2) medication adherence and health literacy and/or numeracy were measured, and methods of measurement were described, (3) aim is to determine association between health literacy and/or numeracy and medication adherence on glucose-lowering agents or medication adherence as part of diabetes self-care behaviors/management, and (4) participants were adults at least 18 years old diagnosed with T2DM. Studies were excluded if no full-text article was available, the article is non-English and cannot be translated clearly even after using

translator applications, the participants only included patients with Type 1 diabetes mellitus, or the results for patients with Type 1 and Type 2 diabetes mellitus were combined and cannot be analyzed separately. Conference papers, review articles, editorials, letters, opinion papers, general practice papers, meta-analyses, a dual publication, and protocol-only papers were not included. The flow diagram for the review was used to identify the eligible articles for the review (Figure 1).

2.3. Data Extraction and Risk of Bias Assessment

Studies were completely reviewed, and the following data were extracted: study-specific characteristics (country, funding source, conflict of interest), study design, practice setting, characteristics of sample (sex ratio, age, race/ethnicity, language), sample size, sampling method, glucose-lowering agent studied and other medications, health literacy and/or numeracy measures and results, medication adherence measure and results, measure of association between medication adherence and health literacy and/or

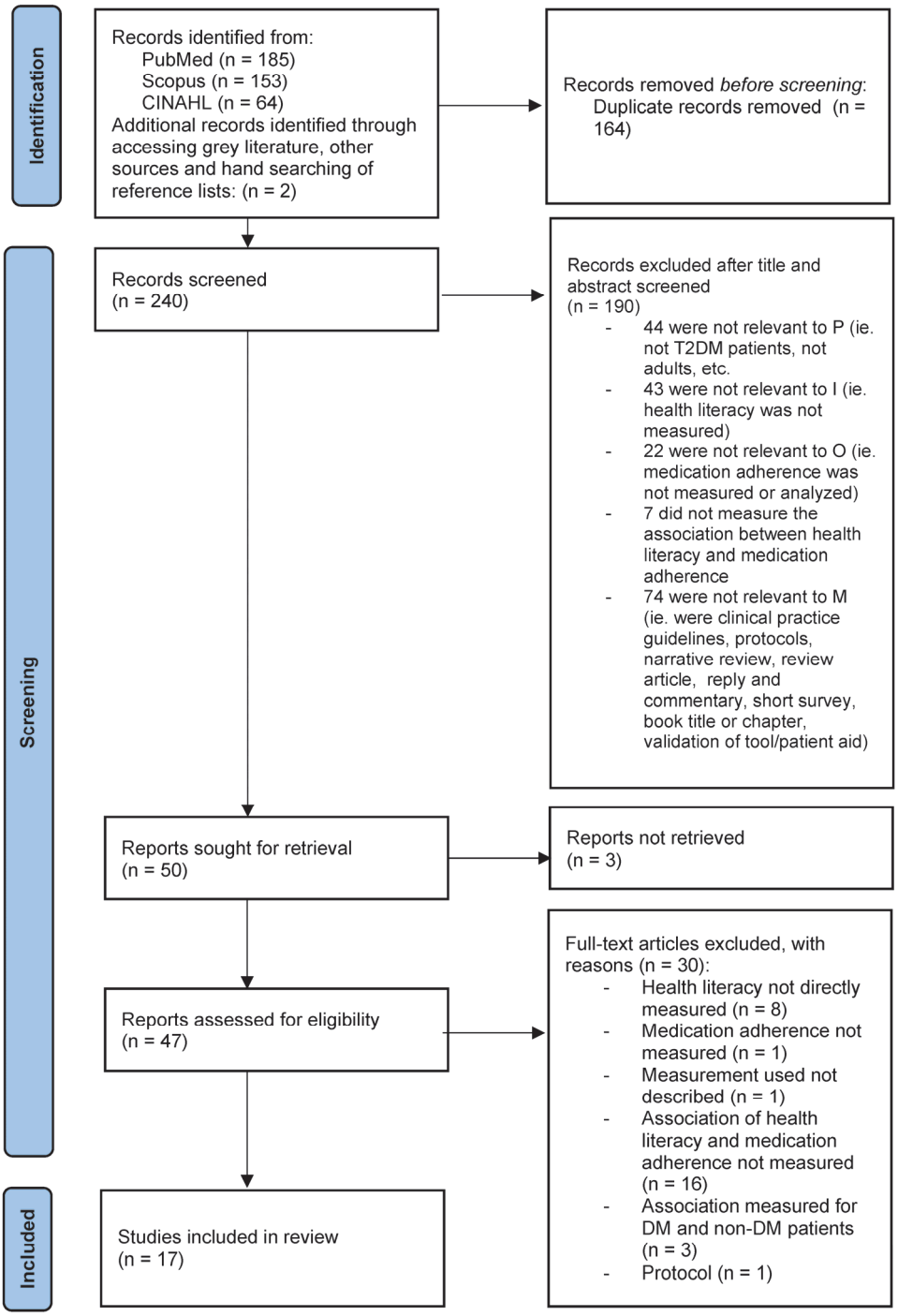

Figure 1. Flow diagram for search process and study selection.

numeracy (correlation coefficient, regression coefficient odds ratio), and covariates adjusted for during analysis. Data extraction was primarily done by one author (KG) and reviewed by the other authors (MG, IP).

The characteristics of all included studies were analyzed through a narrative summary of evidence presented in both text and tabular forms. Also, this review grouped and summarized the results of at least 3 studies that used the same measures on the following variables: 1) health literacy, 2) numeracy, and 3) medication adherence. The median and range of these variables were obtained and tabulated. Any study with missing summary statistic was not included in the summarized results based on the measures used.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) adapted for cross-sectional and cohort studies (Wells et al., n.d.). The studies were rated as good, fair, and poor. A "good" quality study needs to have 3, 4 or 5 stars in the selection domain,1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/ exposure domain. A "fair" quality study has 2 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain. A "poor" quality score is equivalent to 0 or 1 star in the selection domain, 0 stars in the comparability domain, or 0 or 1 stars in the outcome/exposure domain. One author (KG) assessed each study using the NOS while two authors (MG and IP) independently reviewed the initial assessment. Any disagreements on the assessment of each included study were discussed by the three authors until a resolution is reached. A detailed risk of bias assessment plan can be accessed through Appendix A.

3. Results

3.1. Study Selection

Initial search through databases and additional searching in reference lists, existing systematic reviews, and grey literature yielded 404 records. After eliminating 164 duplicate records, 240 records went through title and abstract screening for relevance to the objective. A total of forty-seven articles were reviewed for eligibility after retrieving the full-text articles. Seventeen studies were included in the review upon application of the eligibility criteria (Figure 1). Data from these articles were extracted and summarized. All studies were subjected to a risk of bias assessment to establish its quality.

3.2. Descriptive Analysis

Among the 17 studies included, eight studies were published between 2011 to 2017, three studies in 2018 (Huang et al., 2018a; Huang et al., 2018b; Nandyala et al., 2018) and four in 2019 (Garcia et al., 2019; Hussain et al., 2020; Luz et al., 2019; Ueno et al., 2019), and two studies just last 2020 (Ji et al., 2020; Tefera et al., 2020). All studies employed observational study design, particularly cross-sectional studies (n = 16) and a prospective cohort study completed within 6 months (n = 1; Ueno et al., 2019).

Most studies only used one site of implementation namely, primary care clinics (n = 9), outpatient clinics in hospitals (n = 5), and specialty centers/clinics (n = 2). Only one study implemented its data collection in two sites: a primary care clinic and a specialty clinic (Osborn et al., 2011). Most studies were conducted in United States while the other studies were conducted in Gaza Strip (Elsous et al., 2017), Pakistan (Hussain et al., 2020), China (Ji et al., 2020), Brazil (Luz et al., 2019), Ethiopia (Tefera et al., 2020), and Japan (Ueno et al., 2019) which contributed to the varied race/ ethnicity of the participants in this review.

The number of participants in most of the studies range from 100 to 700 individuals with only one study having less than 100 individuals (Luz et al., 2019) and one study exceeding 1,000 individuals (Fan et al., 2016). Most of the studies had a minimum age of 18 for its participants while four (Huang et al., 2018a; Huang et al., 2018b; Shiyanbola et al., 2018) and two (Elsous et al., 2017; Luz et al., 2019) studies had 20 and 30 years old as the minimum age for participation, respectively. Only one report specifically studied elderly patients who were at least 60 years old (Hussain et al., 2020).

Ten studies included information on the diseases of the participants aside from T2DM while seven studies only focused on T2DM. Only one study included the presence of cardiovascular risk factors among its participants (Garcia et al., 2019). Twelve studies gathered information on the type of glucose-lowering medications of the participants while one study excluded individuals who were on insulin (Garcia et al., 2019). The other studies did not specify the type of diabetes medications of its participants. Also, five studies (Huang et al., 2018a; Nandyala et al., 2018; Osborn et al., 2011; Thurston et al., 2015; Ueno et al., 2019) only considered glucose-lowering medications of the participants while four studies (Huang et al., 2018b; Hussain et al., 2020; Ji et al., 2020; Shiyanbola et al., 2018) included other medications. The rest of the included articles did not explore the number and type of medications the participants were taking. Table 1 summarizes the general characteristics of all included studies.

Various health literacy measures were used with most studies adopting previously validated and common tools available. The health literacy measures in this review include NVS (Newest Vital Sign, n = 5; Huang et al., 2018a; Garcia et al., 2019; Huang et al., 2018b; Shiyanbola et al., 2018; with 1 translated in Chinese, Ji et al., 2020), S-TOFHLA (Short-form Test of Functional Health Literacy in Adults, n = 4; Thurston et al., 2015; Walker et al., 2014; with 1 translated in Spanish, White et al., 2013; and another translated and validated for use in Brazil, Luz et al., 2019), REALM (Rapid Estimate of Adult Literacy in Medicine; n = 2; Bains and Egede, 2011; Osborn et al., 2011), BHLS (Brief Health

Table 1. Summary of the general characteristics of the primary studies included in the review.

#	First Author, Year	Country	Type of Country Income[a]	Classification of WHO Region[b]	Study Setting	Sample Size	Sample Characteristics	Reported Conflict of Interest	Reported Funding Source
1	Bains, 2011	USA	HIC	AMR	Specialty center/clinic	125	T2DM, 50.7% have age between 18 to <65 and 49.3% were at least 65 y/o, English speaking	No	No
2	Elsous, 2017	Palestine	LMIC	EMR	Primary care clinic	369	T2DM plus other diseases, mean age of 56.38 ± 10.36 y/o, Palestinian, taking OHAs and/or insulin	Yes	Yes
3	Fan, 2016	USA	HIC	AMR	Primary care clinic	208	T2DM plus other diseases, mean age of 53.0 ± 10.9 y/o, English speaking	Yes	Yes
4	Garcia, 2019	USA	HIC	AMR	Primary care clinic	279	T2DM plus ≥ 2 cardiovascular risk factors, mean age of 55.2 ± 9.8 y/o, Hispanic, using OHAs only	Yes	Yes
5	Huang, 2018a	USA	HIC	AMR	Primary care clinic	174	T2DM, mean age of 58.7 ± 12.8 y/o, English speaking, taking OHAs and/or insulin	Yes	Yes
6	Huang, 2018b	USA	HIC	AMR	Primary care clinic	174	T2DM plus other diseases, mean age of 58.7 ± 12.8 y/o, English speaking, taking OHAs and/or insulin	Yes	No
7	Hussain, 2020	Pakistan	LMIC	EMR	Outpatient clinic in hospital	524	T2DM plus other diseases, mean age of 64 y/o, Pakistani, taking OHAs and/or insulin	Yes	Yes
8	Ji, 2020	China	UMIC	WPR	Outpatient clinic in hospital	207	T2DM plus other diseases, mean age of 56.1 ± 11.4 y/o, Chinese	Yes	Yes
9	Luz, 2019	Brazil	UMIC	AMR	Specialty center/clinic	97	T2DM, 48.5% have age between 39-59 y/o, 50.5% were at least 60 y/o, Brazilian, taking OHAs and/or insulin	No	No
10	Nandyala, 2018	USA	HIC	AMR	Outpatient clinic in hospital	151	T2DM, mean age of 55.3 ± 11.0 y/o, English speaking, taking OHAs and/or insulin	Yes	Yes
11	Osborn, 2011	USA	HIC	AMR	Primary care clinic, specialty center/clinic	398	T2DM with other diseases, mean age of 54.4 ± 13.0 y/o, English speaking, taking OHAs and/or insulin	No	Yes
12	Shiyanbola, 2018	USA	HIC	AMR	Primary care clinic	174	T2DM with other diseases, mean age of 59.7 ± 12.8 y/o, English speaking, taking OHAs and/or insulin	Yes	Yes
13	Tefera, 2020	Ethiopia	LIC	AFR	Outpatient clinic in hospital	400	T2DM plus other diseases, 14.3% have age less than 40 y/o, 76.5% between 40 to 60 y/o, 9.3% greater than 60 y/o, Ethiopian	Yes	Yes
14	Thurston, 2015	USA	HIC	AMR	Primary care clinic	192	T2DM, mean age of 55.4 ± 10.3 y/o, English speaking, taking OHAs and/or insulin	Yes	Yes
15	Ueno, 2019	Japan	HIC	WPR	Outpatient clinic in hospital	148	T2DM plus other diseases, mean age of 67.9 ± 11.0 y/o, Japanese, taking OHAs and/or insulin	Yes	Yes
16	Walker, 2014	USA	HIC	AMR	Primary care clinic	615	T2DM plus other diseases, mean age of 61.3 ± 10.9 y/o, English speaking	Yes	Yes
17	White, 2013	USA	HIC	AMR	Primary care clinic	149	T2DM, median age of 50 (40-60) y/o for limited HL, 46 (38-54) y/o for adequate HL, Hispanics, taking OHAs and/or insulin	No	Yes

[a] HIC: High-income country, UMIC: Upper-middle-income country, LMIC: Lower-middle-income country, LIC: Low-income country
[b] AFR: African Region, AMR: Region of Americas, SEAR: South-East Asian Region, EUR: European Region, EMR: Eastern Mediterranean Region, WPR: Western Pacific Region

Literacy Screen, n = 2; Fan et al., 2016; Nandyala et al., 2018), BRIEF (Brief Health Literacy Screening Tool, n = 1; Elsous et al., 2017), and LAD (Literacy Assessment of Diabetes, n = 1; Hussain et al., 2020). One study adopted a validated tool developed by Ishikawa et al. (2008; Ueno et al., 2019) while one study developed and validated its own health literacy measures (Tefera et al., 2020). One of these tools explored two domains of health literacy (functional and communicative; Tefera et al., 2020) while one health literacy measure measured all domains of health literacy (Ueno et al. 2019).

Only five studies included numeracy in its evaluation. Two studies (Hussain et al., 2020; Osborn et al., 2011) used DNT (Diabetes Numeracy Test) while one study (Nandyala et al., 2018) used SNS (Subjective Numeracy Scale) for the numeracy measures. Two studies used the numeracy subscale of NVS for the numeracy levels of its participants (Huang et al., 2018a; Shiyanbola et al., 2018).

Several medication adherence measures for self-report and objective information were used in the studies. Self-report medication adherence measures included MMAS-8 (8-item Morisky Medication Adherence Scale, n = 6; Huang et al., 2018a; Garcia et al., 2019; Huang et al., 2018b; Shiyanbola et al., 2018; Thurston et al., 2015; Walker et al., 2014), MMAS-4 (4-item Morisky Medication Adherence Scale, n = 3; Bains and Egede, 2011; Elsous et al., 2017; Fan et al., 2016), SDSCA (Summary of Diabetes Self-care Activities Measure, n = 3 with 1 in Chinese, Ji et al., 2020; 1 in Spanish, White et al., 2013; and 1 using the medication adherence subscale only, Osborn et al., 2011), ARMS-D (Adherence to Refills and Medications Scale for Diabetes, n = 1; Nandyala et al., 2018), BARS (Brief Adherence Rating Scale, n = 1; Hussain et al., 2020), DSCAQ (Diabetes Self-Care Activity Questionnaire, n = 1 validated for used in Brazil; Luz et al., 2019), and 4-item Morisky Green Levine Scale (n = 1; Tefera et al., 2020). One study adopted a previously validated 12-item medication adherence scale (Ueno et al., 2019). Some of the medication adherence measures include the measurement of other diabetes self-care behaviors/management aside from medication adherence (SDSCA and DSCAQ). The two studies that applied objective measures of medication adherence used PDC (Proportion of Days Covered, n = 1; Garcia et al., 2019) and CMG (Cumulative Medication Gap, n = 1; Thurston et al., 2015).

3.3. Association of Health Literacy and Numeracy with Medication Adherence

Among the studies that used a cross-sectional study design, three studies found an association between health literacy and medication adherence (Fan et al., 2016; Osborn et al., 2011; Tefera et al., 2020). Fan et al. (2016) established that limited health literacy is associated with an increased overall non-adherence as well as participants with limited health literacy being more likely to be unintentionally non-adherent. Osborn et al. (2011) stated that health literacy has a direct effect on medication adherence while Tefera et al. (2020) found an association between health literacy and medication adherence. The two studies that used both subjective and objective measures for medication adherence found no association with health literacy (Garcia et al., 2019; Thurston et al., 2015), but Thurston et al. (2015) was able to find a positive relationship between health literacy and ability to remember taking medications only.

Among the five studies that assessed the association of both health literacy and numeracy with medication adherence, only two studies observed significant association (Hussain et al., 2020; Nandyala et al., 2018). Moreover, one study found an association between numeracy and medication adherence, but no association between document literacy and medication adherence (Huang et al., 2018a).

The only study with a prospective cohort design observed a significant positive link between health literacy and medication adherence at baseline, month 3, and month 6 of the study (Ueno et al., 2019). A contradicting result observed by White et al. (2013) was the association of limited health literacy with better medication adherence while there was a non-significant trend between high health literacy and a greater probability of non-adherence. The study characteristics for their methods and results are summarized in Table 2.

Among the studies that used the same measure or tool for health literacy and reported the results, only studies that used NVS to measure health literacy were synthesized. The included studies were Huang 2018a, Huang 2018b, Ji 2020, and Shiyanbola 2018. The median of the health literacy of these studies was a score of 3.7 (2.0–3.7) which corresponds to adequate health literacy. Due to the few studies that evaluated numeracy and the different measures used, there was not enough studies to synthesize the numeracy levels. Studies that used the same measure for medication adherence and reported the results were synthesized in Table 3. In both MMAS-4 and MMAS-8, the medians of the included studies correspond to a medium adherence.

3.4. Study Quality

Most of the cross-sectional studies and the cohort study included participants that were truly or somewhat representative of the target population. Studies that only included a selected group of participants mostly had limited sites for implementation which reduced its ability to represent the target population of the study. Also, most of the studies implemented purposive or convenience sampling. Studies that included participants who were truly representative of the target population were able to implement simple random sampling. Only some of the studies were able to describe and justify the sample size of the participants which reduces the ability to determine its appropriateness for the study. Almost all of the cross-sectional studies with the exception of the study by Fan et al. (2016) did not describe the characteristics of its non-responders which made the comparability of the

Table 2. Summary of the methods and results of the primary studies included in the review.

#	First Author, Year	Sampling technique	Health Literacy Measure[a]	Health Literacy Value	Numeracy Measure[b]	Numeracy Value	Medication Adherence Measure[c]	Medication Adherence Value	Association of Health Literacy and Numeracy and Medication Adherence	Limitations and assumptions in methods
1	Bains, 2011	Purposive	REALM	Mean number correct: 6.1 ± 0.3	–	–	MMAS-4	Mean score: 0.9 ± 0.1	Not significantly associated (bivariate analysis: $r = 0.025$, $p = 0.784$; adjusted for covariates: $\beta = -0.17$, 95% CI –0.09 to 0.05)	Causality among variables cannot be confirmed; conducted in a single academic center only
2	Elsous, 2017	Simple random	BRIEF	Mean score: 2.9 ± 0.59	–	–	MMAS-4	Highly adherent: 58% Medially adherent: 39.5% Low adherence: 2.5%	Not associated (OR = 1.994, 95% CI 0.684 to 5.812)	Over-estimation of medication adherence due to self-reporting; limited participant information; selection bias
3	Fan, 2016	Purposive	BHLS	Adequate HL: 36.5% Limited HL: 63.5%	–	–	MMAS-4	Overall medication nonadherence: 1.3% Unintentional nonadherence: 55.3% Intentional nonadherence: 39.9%	In bivariate analysis, limited health literacy is associated with increased overall non-adherence ($\beta = 0.39$, $p = 0.037$). In multivariable analysis, limited health literacy patients are more likely to be unintentionally non-adherent (OR = 1.87, 95% CI 1.01 to 3.49, $p < 0.05$).	Causality among variables cannot be confirmed; overall medication adherence, not adherence to diabetes medications, is assessed; limited generalizability
4	Garcia, 2019	Purposive	NVS	Adequate HL: 9% Limited HL: 91%	–	–	MMAS-8	Low: 49.8% Medium: 21.5% High: 28.7%	No association between health literacy and MMAS reported adherence ($p = 0.51$) and PDC measured adherence ($p = 0.35$).	Causality among variables cannot be confirmed; limited generalizability; limited factors to poor adherence considered
							PDC	Low: 72% Medium: 23.3% High: 4.7%		
5	Huang, 2018a	Purposive	NVS	Overall HL: 3.7 ± 2.0 Document literacy: 1.5 ± 0.8	NVS	Numeracy: 2.3 ± 1.5	MMAS-8	Mean score: 2.3 ± 1.5 Low (score < 6): 71 ± 40.8 Medium (score = 6 to < 8): 61 ± 35.1 High (score = 8): 42 ± 24.1	Document literacy is not associated ($r_s = -0.054$, $p > 0.05$), but numeracy is associated with medication adherence ($r_s = 0.180$, $p < 0.05$)	Causality among variables cannot be confirmed; limited generalizability
6	Huang, 2018b	Purposive	NVS	Mean score: 3.7 ± 2.0 Inadequate: 17.8% Marginal: 22.4% Adequate: 59.8%	–	–	MMAS-8	Low: 40.8% Medium: 35.1% High: 24.1%	Not significantly associated (bivariate analysis: $r = 0.12$, $p > 0.05$; adjusted for covariates: $\beta = -0.04$, $p = 0.586$)	Causality among variables cannot be confirmed; limited generalizability; over-estimation of medication adherence due to self-reporting

Table 2. Summary of the methods and results of the primary studies included in the review (continued).

#	First Author, Year	Sampling technique	Health Literacy Measure[a]	Health Literacy Value	Numeracy Measure[b]	Numeracy Value	Medication Adherence Measure[c]	Medication Adherence Value	Association of Health Literacy and Numeracy and Medication Adherence	Limitations and assumptions in methods
7	Hussain, 2020	Purposive	LAD	0–20: 47% 21–40: 78% 41–60: 10%	DNT	Nutrition: 52.5% correct Exercise: 62.9% correct Blood glucose monitoring: 71.5% correct Oral medications: 69.1% correct Insulin: 49.9% correct	BARS	Mean score: 3.1 ± 0.5	Significantly associated; individuals with adequate literacy had fewer days of skipping medicines ($\chi^2(2) = 11.6$, $p = 0.04$) and more likely to not take less than the prescribed dose ($\chi^2(2) = 11.13$, $p = 0.02$) compared with those of inadequate health literacy.	Small sampling size; sampling bias; possibility of participants supplying false information
8	Ji, 2020	Purposive	NVS (Chinese)	Mean score: Average: 3.1 ± 0.5	–	–	SDSCA (Chinese)	Total: 40.1 ± 11.6 Adequate SDSCA: 16.4% Medication treatment: 6.4 ± 1.7	Not associated (univariate analysis: B = –0.17, $p = 0.67$; correlation model: $r = -0.03$)	Causality among variables cannot be confirmed; conducted in an endocrinology center only; some instruments not tested previously among Chinese T2DM patients
9	Luz, 2019	Simple random	B-TOFHLA	Inadequate: 47.4% Marginal: 22.7% Adequate: 29.9%	–	–	DSCAQ	OHAs: 6.22 ± 2.05 Insulin: 6.22 ± 2.05 Indicated pills: 6.75 ± 1.12	Not associated with taking diabetes medications ($p = 0.35$) or insulin ($p = 0.46$) as recommended or taking the indicated number of diabetes pills ($p = 0.84$)	Causality among variables cannot be confirmed; recall bias
10	Nandyala, 2018	Purposive	BHLS	Overall: 12.1 ± 1.3 Group with suboptimal medication adherence: 12 ± 1.4 Group with optimal medication adherence: 12.5 ± 0.9	SNS	Overall: 4.5 ± 1 Group with suboptimal medication adherence: 4.4 ± 1.1 Group with optimal medication adherence: 4.9 ± 0.8	ARMS-D	Overall: 39.6 ± 4.2 Group with suboptimal medication adherence: 38.6 ± 4 Group with optimal medication adherence: 44 ± 0	Significantly associated (health literacy: $U = 1{,}303$, $p = .027$; numeracy: $U = 1{,}200$, $p = .012$)	Causality among variables cannot be confirmed; conducted in a single academic center only; limited generalizability
11	Osborn, 2011	Purposive	REALM	Overall: 58.9 ± 12.7 < 9th grade: 31% ≥ 9th grade: 69%	DNT	Mean score: 60.0 ± 0.24	SDSCA (medication adherence subscale only)	Mean score: 6.7 ± 1.0	Health literacy has a direct effect on medication adherence ($r = 0.12$, $p < 0.02$) but only marginally associated in the trimmed model ($r = 0.10$, $p = 0.06$). Diabetes-related numeracy is not associated with medication adherence ($r = -0.09$).	Only self-report measure was used for adherence; only associations, not causality, are observed

Table 2. Summary of the methods and results of the primary studies included in the review (continued).

#	First Author, Year	Sampling technique	Health Literacy Measure[a]	Health Literacy Value	Numeracy Measure[b]	Numeracy Value	Medication Adherence Measure[c]	Medication Adherence Value	Association of Health Literacy and Numeracy and Medication Adherence	Limitations and assumptions in methods
12	Shiyanbola, 2018	Purposive	NVS	Overall: 3.7 ± 2.0 Document literacy: 1.5 ± 0.8	NVS	Numeracy: 2.3 ± 1.5	MMAS-8	Mean score: 5.9 ± 1.9	No direct relationship (unstandardized: β = 0.002; standardized: β = 0.002; p = 0.989) Document literacy (unstandardized: β = –0.218; standardized: β = –0.099; p = 0.138) and numeracy (unstandardized: β = 0.107; standardized: β = 0.087; p = 0.241) have no direct relationship with medication adherence	Limited generalizability; over-estimation of medication adherence due to self-reporting; clinical markers not controlled during data analysis
13	Tefera, 2020	Simple random	15-item diabetic health literacy scale	Overall mean diabetic health literacy score: 3.68 ± 0.82 High diabetic HL (score ≥75%): 56.5% Moderate diabetic HL (score 60-74%): 26.3% Low diabetic HL (score <59%): 17.3%	–	–	Morisky Green Levine Scale	Good adherence (0 pt): 34% Moderate adherence (1-2 pts): 56.3% Poor adherence (3-4 pts): 9.8%	Associated (p = 0.023)	Causality among variables cannot be confirmed; conducted on outpatients of one hospital only
14	Thurston, 2015	Purposive	S-TOFHLA	Overall: 25.5 ± 10.5 Limited health literacy: 32.8% Adequate health literacy: 67.2%	–	–	MMAS-8	Overall: 5.5 ± 1.8 Low: 58.9% Medium: 27.1% High: 14%	Health literacy is not significantly correlated to MMAS reported and CMG measured adherence, but patients lower health literacy level experience greater difficulty remembering to take medications compared with more health-literate patients (p = 0.017).	Causality among variables cannot be confirmed; non-representative of the indigent population as a whole; other diabetes-related factors not controlled during analysis
							CMG	Overall: 0.33 ± 0.24 Adherent: 34.9% Nonadherent: 65.1%		
15	Ueno, 2019	Simple random	Adopted validated tool that measured functional, communicative, and critical health literacy	Not reported	–	–	12-item version of Medication Adherence Scale	Not reported	Significant positive link (baseline: 0.29; after 3 months: 0.17; after 6 months: 0.19; all at 5% significance)	Conducted in one university hospital only; response bias of participants with the self-report measures

Table 2. Summary of the methods and results of the primary studies included in the review (continued).

#	First Author, Year	Sampling technique	Health Literacy Measure[a]	Health Literacy Value	Numeracy Measure[b]	Numeracy Value	Medication Adherence Measure[c]	Medication Adherence Value	Association of Health Literacy and Numeracy and Medication Adherence	Limitations and assumptions in methods
16	Walker, 2014	Purposive	S-TOFHLA	Not reported	–	–	MMAS-8	Not reported	Not associated with marginal medication adherence (β = 0.58) and adequate medication adherence (β = 0.26)	Causality among variables cannot be confirmed; additional confounding factors may be present; only conducted in one part of the US
17	White, 2013	Purposive	S-TOFHLA (Spanish)	Not reported	–	–	SDSCA (Spanish)	Not reported	Limited health literacy is associated with better medication adherence (χ^2 = 0.04, $p < 0.05$) Non-significant trend between high health literacy and greater probability of non-adherence (AOR = 1.6, 95% CI 0.9 to 0.3, p = 0.11)	Causality among variables cannot be confirmed; small sample size; response bias which cause over-reporting among Hispanics

[a] REALM: Rapid Estimate of Adult Literacy in Medicine, NVS: Newest Vital Sign, S-TOFHLA: Short-form Test of Functional Health Literacy in Adults, BHLS: Brief Health Literacy Screen, BRIEF: Brief Health Literacy Screening Tool, LAD: Literacy Assessment of Diabetes
[b] DNT: Diabetes Numeracy Test, SNS: Subjective Numeracy Scale
[c] MMAS-8: 8-item Morisky Medication Adherence Scale, MMAS-4: 4-item Morisky Medication Adherence Scale, SDSCA: Summary of Diabetes Self-care Activities Measure, ARMS-D: Adherence to Refills and Medications Scale for Diabetes, BARS: Brief Adherence Rating Scale, DSCAQ: Diabetes Self-Care Activity Questionnaire, PDC: Proportion of Days Covered, CMG: Cumulative Medication Gap

Table 3. Medication adherence of included studies grouped per measure or tool used.

Medication Adherence Measure	Included Studies	Median (Range)
MMAS-4	Bains 2011 Elsous 2017 Fan 2016	0.9 (0.6–2)
MMAS-8	Huang 2018a Huang 2018b Shiyanbola 2018 Thurston 2015	5.7 (2.3–5.9)

responders and non-responders unsatisfactory. The cohort study was able to describe how the selection of the non-exposed cohort was from the same source as the exposed cohort.

Almost all of the studies used a validated measurement tool for health literacy/numeracy except for a study that used a non-validated but accessible measurement tool (Tefera et al., 2020). Furthermore, all studies used a validated medication adherence self-report tool or another method for an objective measurement of medication adherence, with some studies implementing a multi-measure strategy for medication adherence. Based on the NOS used for this study, medication adherence reported through record linkage (counting of pills/refills) were assigned with two stars for the outcome domain while studies that reported adherence using self-report only were assigned with one star. This is due to the inherent reporting bias when self-reporting is done to measure medication adherence.

To ensure comparability of the participants in different outcome groups, some studies controlled for several confounding factors in the statistical analysis. Eight of the cross-sectional studies controlled for the most important factors – age and education level. Aside from the two factors, most of the studies controlled for several other confounding factors such as sex, race, and income status. The number and types of confounding factors adjusted for varied greatly from one study to another. All studies that did not control for any confounders had a poor-quality score.

Almost all of the studies described the statistical tests used for the analysis. These were found to be appropriate with the results of the statistical analysis available in the article. The only study that did not present the measure of association completely received a poor-quality score.

Aside from the previously mentioned assessment results for the only cohort study included, the study described and measured the exposure (health literacy) at baseline which immediately showed that the exposure was present at the start of the study. However, the study was able to ensure sufficient follow-up period to ensure that a change in medication adherence can be observed and with 95% of the participants retained until the completion of the study.

Overall, there were six (Fan et al., 2016; Huang et al., 2018a; Huang et al., 2018b; Ji et al., 2020; Nandyala et al., 2018; Osborn et al., 2011) cross-sectional studies that had a good quality score and four (Bains and Egede, 2011; Garcia et al., 2019; Shiyanbola et al., 2018; White et al., 2013) with fair quality score based on the NOS. Studies with a poor-quality score included six cross-sectional studies (Elsous et al., 2017; Hussain et al., 2020; Luz et al., 2019; Tefera et al., 2020; Thurston et al., 2015; Walker et al., 2014) and the only prospective cohort study (Ueno et al., 2019). The comprehensive risk of bias assessment can be found in Table 4.

4. Discussion

4.1. Main Findings

Based on our study, this is the first review to comprehensively describe in detail the association of health literacy and numeracy with medication adherence among Type 2 diabetic patients across several nationalities. Out of the seventeen articles that studied the association of health literacy and medication adherence, only four studies found a significant association and direct effect of health literacy on medication adherence (Fan et al., 2016; Osborn et al., 2011; Tefera et al., 2020; Ueno et al., 2019). One study found only a positive association between one question in the health literacy tool used and medication adherence, but the overall health literacy of participants was not correlated with adherence (Thurston et al., 2015). Among the five included reports that looked at the association of both health literacy and numeracy with medication adherence, two studies observed significant association of both exposures with medication adherence (Hussain et al., 2020; Nandyala et al., 2018) while one study only observed significant association between numeracy and medication adherence (Huang et al., 2018a).

One of the studies reported significant association between health literacy and medication adherence that were inconsistent with the other studies. Based on the study of White et al. (2013), limited health literacy, not adequate health literacy, was associated with better medication adherence. The results of this study need to be interpreted with caution given the limited sampling frame and it did not control for education level.

4.2. Interpretation

The varying results of the included studies in this review regarding the association of health literacy/numeracy with medication adherence can be explained by the differences in population, practice setting, and methodology used in the studies. Since there are no exclusion criteria pertaining to the sample characteristics of T2DM patients, the included reports have a wide variety of participants. Furthermore, the current review included studies that may have participants on oral hypoglycemic agents and/or insulin for their glucose-lowering therapy. Since most diabetic patients shift from one

Table 4. Risk of bias assessment using the adapted Newcastle-Ottawa Quality Assessment Scale criteria for cross-sectional and cohort studies.

Cross-sectional Study Design

Author (Year)	Selection				Comparability	Outcome		Quality Score
	Representativeness of Sample	Sample Size Justified & Satisfactory	Non-respondents	Ascertainment of Exposure		Ascertainment of Outcome	Statistical Test	
Bains & Egede (2011)	Selected group. Participants were predominantly minority (71.4% black but none of the participants was of Hispanic or other racial origin), but not all have low income (35.8% have income of $15,000+). Also, income status and race were not part of the inclusion criteria.	No	No mention of non-respondents.	Used a validated measurement tool for health literacy (REALM) ★★	Age, education (≤ or > high school graduate), sex, race, income, and health status (better, same, or worse as last year) were adjusted for multiple regression models. ★★	Medication adherence self-report (MMAS-4) ★	Spearman's correlation tested association between the variables and multiple regression models were used to assess the independent associations. ★	Fair
Elsous et al. (2017)	Participants were truly representative of type 2 DM patients attending primary health care clinics in the Gaza Strip, Palestine. Cluster sampling was done to select a PHC from each governate in the Gaza Strip. Then, sampling was done proportionally and randomly to achieve representativeness of sample and gender. ★	Yes ★	No mention of non-responders.	Used a validated measurement tool for health literacy (BRIEF) ★★	No confounding factors were controlled in logistic regression.	Medication adherence self-report (MMAS-4) ★	Logistic regression for health literacy predicted medication adherence. ★	Poor
Fan et al. (2016)	Somewhat representative of the target population. Participants were recruited through purposive sampling of eligible participants. Also, only 2 races were included (26.4% Caucasian, 73.6% African-American) with 22.5% having an income of ≥$20,000. ★	Yes ★	Respondents and non-respondents are comparable, and response rate is high (≥ 73.2%) ★	Used a validated measurement tool for health literacy (BHLS) ★★	Age, gender, race, insurance, medication regimen complexity, and depression were adjusted for in bivariate regressions. ★	Medication adherence self-report (MMAS-4) ★	Linear regressions were done on overall medication adherence while logistic regressions were done for unintentional and intentional adherence. ★	Good
Garcia et al. (2019)	Selected group. Participants were recruited from only one Federally Qualified Health Center in the south most region of San Diego County California near the U.S./Mexico Border.	No	No mention of non-responders.	Used a validated measurement tool for health literacy (NVS) ★★	Age, education level, gender, country of birth, preferred language of interview, employment status, marital status, income, CVD risk factors, and HbA1c were adjusted for in bivariate analyses. ★★	Objective measure (PDC) and medication adherence self-report (MMAS-4) ★★	Bivariate analyses (Chi-square and ANOVA tests) assessed the association between variables. ★	Fair
Huang et al. (2018a)	Somewhat representative of the target population. Participants were recruited through purposive sampling of eligible participants in the two family medicine clinics. ★	No	Comparability between respondents and non-respondents is unsatisfactory. Only the response rate is available (87.4%).	Used a validated measurement tool for health literacy and numeracy (NVS) ★★	Age, education, gender, and race were adjusted for in the path analysis and test of moderation effect of medication self-efficacy only. ★★	Medication adherence self-report (MMAS-8) ★	Spearman's correlation tested association between the variables. ★	Good

Table 4. Risk of bias assessment using the adapted Newcastle-Ottawa Quality Assessment Scale criteria for cross-sectional and cohort studies (continued).

Author (Year)	Selection				Comparability	Outcome		Quality Score
	Representativeness of Sample	Sample Size Justified & Satisfactory	Non-respondents	Ascertainment of Exposure		Ascertainment of Outcome	Statistical Test	
Huang et al. (2018b)	Somewhat representative of the target population. Participants were recruited through purposive sampling of eligible participants in the two family medicine clinics. ★	No	Comparability between respondents and non-respondents is unsatisfactory. Only the response rate is available (87.4%).	Used a validated measurement tool for health literacy (NVS) ★★	Demographics (age, highest education level, gender, race, health insurance, and annual household income), and diabetes- and health-related factors were adjusted for in bivariate correlations and multiple linear regressions. ★★	Medication adherence self-report (MMAS-8) ★	Bivariate correlations tested univariate relationships between the variables and multiple linear regressions were used to assess the independent associations. ★	Good
Hussain et al. (2020)	Selected groups. Participants were not representative of older female patients with Type 2 DM in Pakistan. Only two private sector hospital centers located in Lahore, Pakistan were the included.	No	Comparability between respondents and non-respondents is unsatisfactory. Only the response rate is available (95.3%).	Used a validated measurement tool for health literacy (LAD) and numeracy (DNT) ★★	No confounding factors were controlled in bivariate association and linear regression.	Medication adherence self-report (BARS) ★	Bivariate analysis is used to assess the relationship between health literacy and medication adherence. ★	Poor
Ji et al. (2020)	Somewhat representative of the target population. Participants were recruited through convenience sampling of eligible participants in the outpatient clinic of a tertiary hospital in a suburban area in Beijing, China. ★	Yes ★	No mention of non-responders.	Used a validated measurement tool for health literacy (NVS) ★★	Age, level of education, gender, duration of diabetes, number of prescribed medications, and number of comorbidities were adjusted for in multiple regression models. ★★	Medication adherence self-report (SDSCA) ★	Univariate and multiple logistic regression were done on the variables. ★	Good
Luz et al. (2019)	Participants were truly representative of type 2 DM patients treated at a referral center in the city of Recife. Simple random sampling was drawn from the outpatient appointment list with consideration of the inclusion criteria. ★	Yes ★	No mention of non-responders.	Used a validated measurement tool for health literacy (B-TOHFLA) ★★	No confounding factors were controlled in the Chi-square test.	Medication adherence self-report (DSCAQ) ★	Chi-square test was used to determine association between functional health literacy and diabetes self-care. ★	Poor
Nandyala et al. (2018)	Somewhat representative of the target population. Participants were recruited through purposive sampling with the exclusion criteria of not having a a "My Health at Vanderbilt" patient portal account and not having a mobile phone or computer with Internet access. ★	No	No mention of non-responders.	Used a validated measurement tool for health literacy (BHLS) and numeracy (SNS) ★★	Age, education, gender, race, income, insurance status, insulin use, duration of diagnosed diabetes, and the number of prescribed diabetes medications were adjusted for bivariate analyses and logistic regression models. ★★	Medication adherence self-report (ARMS-D) ★	Mann-Whitney U test, Chi-square test, and logistic regressions were done to examine differences among participants and examine relationships between the variables. ★	Good

Table 4. Risk of bias assessment using the adapted Newcastle-Ottawa Quality Assessment Scale criteria for cross-sectional and cohort studies (continued).

Author (Year)	Selection				Comparability	Outcome		Quality Score
	Representativeness of Sample	Sample Size Justified & Satisfactory	Non-respondents	Ascertainment of Exposure		Ascertainment of Outcome	Statistical Test	
Osborn et al. (2011)	Somewhat representative of the target population. Participants were recruited through purposive sampling of eligible participants from 2 primary care clinics and 2 endocrinology clinics. Only 2 racial status were considered in the study, namely: White (65.0%) and African-American (35.0%). ★	No	Comparability between respondents and non-respondents is unsatisfactory. Only the response rate is available (98%).	Used a validated measurement tool for health literacy (REALM) and numeracy (DNT) ★★	Age, education, gender, income, insulin use, diabetes type, and duration of diabetes were adjusted in the series of path analytic models. ★★	Medication adherence self-report (SDSCA) ★	Series of path analytic models were done to test for associations. ★	Good
Shiyanbola et al. (2018)	Selected groups. Participants were not representative of type 2 DM patients in the USA. Only two family medicine clinics in a Midwestern State in the United States were included in the study and used convenience sampling of eligible invidividuals based on the electronic health record database of the clinics.	No	Comparability between respondents and non-respondents is unsatisfactory. Only the response rate is available (87.4%).	Used a validated measurement tool for health literacy and numeracy (NVS) ★★	Age, education, self-efficacy, sex, race, number of medications, and number of illness were adjusted for in the regression models. ★★	Medication adherence self-report (MMAS-8) ★	Linear regression models were used on the variables to examine association. ★	Fair
Tefera et al. (2020)	Participants were truly representative of type 2 DM patients attending the outpatient clinic at the University of Gondar Comprehensive specialized hospital in Northwest Ethiopia. Simple random sampling was used to select the study participants. ★	Yes ★	No mention of non-responders.	Non-validated measurement tool, but tool is available from another article ★	No confounding factors were controlled in Chi-square tests.	Medication adherence self-report (Morisky Green Levine Scale 4 item adherence assessment tool) ★	Pearson Chi-square test was done to examine the association of the variables. ★	Poor
Thurston et al. (2015)	Somewhat representative of the target population. Participants were recruited through purposive sampling in three clinical sites for underserved patients in Athens and the metro-Atlanta communities in Georgia. ★	Yes ★	No mention of non-responders.	Used a validated measurement tool for health literacy (S-TOHFLA) ★★	No confounding factors were controlled in the correlation and regression models.	Objective measure (CMG) and medication adherence self-report (MMAS-8) ★★	Linear and logistical regression were done on the variables to test for association. ★	Poor
Walker et al. (2014)	Somewhat representative of the target population. Participants were recruited through purposive sampling from adult primary care clinics of an academic medical center and a Veterans Affairs Medical Center in the Southeastern US. ★	Yes ★	No mention of non-responders.	Used a validated measurement tool for health literacy (S-TOHFLA) ★★	Age, sex, race/ethnicity, marital status, health literacy and comorbidity were controlled as applicable. ★	Medication adherence self-report (MMAS-8) ★	Pearson's correlation was used in determining the association in the variables, but only the beta coefficient were shown.	Poor
White et al. (2013)	Selected groups. Patients are not representative of type 2 DM patients who are Hispanics with limited resources. Only three centers in Nashville, Tennessee that serve a Hispanic population were included in the study.	No	Comparability between respondents and non-respondents is unsatisfactory. Only the response rate is available (94%).	Used a validated measurement tool for health literacy (S-TOHFLA) ★★	Age, gender, income, and insurance status were adjusted for in the multivariable logistic regression model. ★	Medication adherence self-report (SDSCA) ★	Multivariable logistic regression model assessed for the independent association of the variables. ★	Fair

Table 4. Risk of bias assessment using the adapted Newcastle-Ottawa Quality Assessment Scale criteria for cross-sectional and cohort studies (continued).

Cohort Study Design

Author (Year)	Selection				Comparability	Outcome			Quality Score
	Representativeness of Exposed Cohort	Selection of the non-exposed cohort from the same source as exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Was follow-up long enough for outcomes to occur (≥ 6 months)	Adequacy of follow-up of cohorts	
Ueno et al. (2019)	Participants were truly representative of type 2 DM patients attending the outpatient internal medicine department for diabetes metabolism at a hospital in Tokyo. Simple random sampling was used to select the study participants. ★	Yes ★	Patients answered a validated self-report tool for health literacy	No (health literacy was present and measured at baseline)	No factors were controlled for in the covariance structure analysis.	Medication adherence self-report (adopted tool) ★	Yes ★	96% participated at the 3-month follow-up and 95% participated at the 6-month follow-up. ★	Poor

medication regimen to another, their ability to understand their regimen and adapt with its changes can be explored in relation to how they adhere with their medication regimen (Mosenzon et al., 2016; Wexler, 2021). All of the included reports used validated or reported measures for health literacy and numeracy and medication adherence. Among the eighteen reports in this review, only two studies used a multi-measure approach on medication adherence of its participants (Garcia et al., 2019; Thurston et al., 2015). Combining subjective and objective measures for medication adherence improves the sensitivity of the results and allows researchers to explore the possible factors that contribute to medication adherence. It combines the strengths of self-reporting and usage reporting to monitor how patients manage their diabetes medications. In both studies, health literacy is observed to be not significantly correlated with both subjective and objective adherence (Krass et al., 2015; Nguyen et al., 2014). However, it should be noted that neither study was rated with a good quality score based on the NOS. It is notable to mention that the two studies (Hussain et al., 2020; Tefera et al., 2020) which used diabetes-specific health literacy/numeracy tools were able to observe a significant association between health literacy/numeracy and medication adherence. Most of the validated and commonly used health literacy/numeracy measures were designed for the general population. These results suggest the possible advantage of using disease-specific health literacy/numeracy measures as it increases the sensitivity and reliability of the results when used on diabetic patients. It allows measurement of health literacy/numeracy to reflect the specific health needs among diabetic patients (Nath et al., 2001).

The confounding factors considered as important to be controlled in studies estimating the association of health literacy and/or numeracy with medication adherence are age and education level. Age is a known confounder in the relationship between health literacy and/or numeracy and medication adherence. Several systematic reviews have shown how older adults have lower health literacy (Baker et al., 2000; Chesser et al., 2016). Also, one study observed that the limited perceived health literacy increases by age which consequently negatively affects their functional health literacy and frequency of doctor visits (Berens et al., 2016). Medication adherence is observed to be affected by various factors such as patient characteristics. One systematic review found that medication adherence is lowest in the very old and very young population (Gast and Mathes, 2019) while another study found that medication adherence is higher among older patients along with those living in areas with higher education rates (Rolnick et al., 2013). Not all of the included studies adjusted for confounding factors during its analysis. One study (Hussain et al., 2020) which found a significant association with health literacy/numeracy and medication adherence did not control for confounding factors. However, the primary difference of this study is it only included participants who were at least 60 years old which may eliminate age as a confounder. The positive results of two other studies that did not adjust for any confounders should be interpreted with caution since their inclusion criteria for participants make it inevitable for age and education level to be confounders (Tefera et al., 2020; Ueno et al., 2019). Also, studies that controlled for confounders had varying factors included. Since these studies assessed the association of the same interventions and outcome (health literacy/numeracy and medication adherence), adjusting for different confounders may have affected the accuracy in detecting the association.

The only prospective cohort study included in this review observed a significant positive link between health literacy and medication adherence. In comparison with most of the included cross-sectional studies, its study design suggests that a longitudinal study can better explore the effect of health literacy on medication adherence over time. However, this study was rated with a poor-quality score due to its poor selection strategy and lack of adjustment for the confounding factors.

There are several determinants of medication adherence that have been previously identified. These can be broadly categorized into health system factors, provider behaviors, and patient-related characteristics. Health literacy and numeracy are just two patient-related factors that may affect medication adherence. However, overall medication adherence can be affected by other factors together with health literacy and numeracy. The communication style of the healthcare provider and the ability of the patients to view themselves as partners in their treatment process have been revealed as positively correlated with medication adherence. Disease- and disease management-relevant cognition, perception, and beliefs are shown to be related with adherence as well. The interplay of all these factors all contribute to the medication adherence or non-adherence of the patient. Several models have been developed to illustrate the pathways on how varying factors affect medication adherence (García-Pérez et al., 2013; WHO, 2003).

Aside from having several factors that can affect medication adherence, it is important to look at the different domains of health literacy since all of these domains may have an impact on medication adherence. Most of the available tools to measure health literacy focus on functional health literacy only. The current review included reports that measured two to three domains of health literacy. Among these studies that did not limit the measurement to functional health literacy, two studies found an association between health literacy and medication adherence (Tefera et al., 2020; Ueno et al., 2019). It suggests that the association can be observed if the study is not limited to functional health literacy and highlights the importance of including communicative and critical health literacy in studying associations. It aligns with the findings of Heijmans (2015)

wherein the correlation of communicative and critical health literacy to self-management of chronic diseases were stronger compared with functional health literacy. Diabetes management is not limited to reading the diabetes regimen provided by their prescriber; it is highly reliant on the ability of the diabetic patient to conduct self-management activities in managing their diabetes. Self-management activities will include the ability of the patient to extract, analyze, and apply various information about their disease which involves all domains of health literacy.

The current review explored the impact of numeracy on medication adherence as a closely associated and equally important skill of diabetic patients on their medication adherence. As shown in the reports that included numeracy (Huang et al., 2018a; Hussain et al., 2020; Nandyala et al., 2018; Osborn et al., 2011; Shiyanbola et al., 2018), having adequate health literacy does not necessarily translate to adequate numeracy skills. Among the five reports that included numeracy, three studies found a significant association between numeracy and medication adherence (Huang et al., 2018a; Hussain et al., 2020; Nandyala et al., 2018). Diabetic patients may have difficulties understanding and using the available information regarding diabetes management, but they can interpret the readings on their blood glucose meter during self-monitoring. The conflicting results of these studies may be attributed to the varying methodology implemented with some studies using a separate tool validated to measure numeracy while other studies only used the subscale of the health literacy tool. Furthermore, the medication regimen of the participants varies across the studies with some only taking glucose-lowering medicines while other patients were recorded to also take medicines for other diseases.

4.3. Implications

The results of the review highlight the importance of exploring the impact of health literacy and numeracy along with other patient-related characteristics that may affect medication adherence. Health literacy and numeracy on their own may not affect medication adherence of all T2DM patients, but these are important factors that should still be considered since medication adherence involves multi-factorial strategies to achieve its improvement among T2DM patients. Strategies for improving medication adherence should incorporate relevant variables in the aspect of the provider, patient, and health system.

4.4. Strengths and Limitations

The current review involved a wide literature search to obtain all available relevant studies. Compared with the existing reviews on the effect of health literacy on medication adherence (Chima et al., 2020), this review did not include any limitations on the practice setting, country, and population which increased the diversity of the participants. In studies conducted in the USA alone, the overall health literacy of the participants as well as the proportion of individuals with adequate and inadequate literacy vary. Furthermore, the type of country income of the practice settings in the included studies range from high to low income. This also affects the overall health literacy of the participants in the study. The available systematic review only included eleven representative studies. Other systematic reviews included patients that have other chronic conditions instead of just focusing on diabetes mellitus (Loke et al., 2012, n = 9; Zhang et al., 2014, n = 35). The existing reviews concluded that there is a weak to no clear and consistent association between health literacy and medication adherence. However, their results were already an aggregation of studies with very diverse groups of patients having varying chronic conditions. This increases the variety of factors that affect health literacy and medication adherence. This present review only looks at T2DM patients to establish a more specific association on the variables of interest.

Several limitations of this review can be linked with the availability and quality of the included studies. The current review is only able to include search results which are published in English or can be translated in English during screening and eligibility phase. Moreover, an inherent publication bias is present with this being a systematic review that included analysis of the published reports only. Only the data provided in the published articles were reviewed; there was no attempt to obtain more data from the authors of the included studies. Also, the included study designs were mostly cross-sectional except for one study which was a prospective cohort study. Therefore, long term changes in the effect of health literacy and numeracy on medication adherence cannot be established in this review. Only the association was observed in all of the included studies so a causal relationship between health literacy and numeracy and medication adherence cannot be established. Also, the reporting of the results varies across the included studies although the variables measured are the same. There were studies that did mentioned collection of health literacy/ numeracy and medication adherence of the participants but did not include these in their results (Ueno et al., 2019; Walker et al., 2014).

5. Conclusions

Overall, there are varying results on the association of health literacy and numeracy with medication adherence. Although there are fewer studies where an association was observed, the lack of a standardized methodology in establishing the association and the varying quality scores of the included studies paved the conclusion of no significant association between health literacy and/or numeracy and medication adherence in this current review.

Results of this review suggest the importance of considering all domains of health literacy in future studies.

Also, the current health literacy measures focus on functional health literacy so it will be beneficial for researchers if a validated tool that can measure all three domains of health literacy will be widely available. Tools used in measuring health literacy and numeracy may have to be appropriate and validated for the setting of the study such as use of a validated tool that has been translated to the language of the participants or developing a tool that can be more contextualized to the target population. As for measuring medication adherence, using a multi-measure approach by combining subjective and objective measures can increase the sensitivity and reliability of the results. Other methods for assessing medication adherence could be explored to determine which measure/s will be most appropriate given the setting and sample characteristics (Gonzalez and Schneider, 2011). Considering the varied methodology of the included studies to establish the association of health literacy and numeracy with medication adherence, future studies can explore developing a standardized method for assessing association. This could include guidelines on which confounders have to be considered when establishing association considering that there are numerous confounders of health literacy, numeracy, and medication adherence. Prospective cohort studies may better establish a causal relationship between health literacy and/or numeracy and medication adherence especially when interventions to improve health literacy and/or numeracy will be used. Due to the varying results on the association of health literacy and numeracy with medication adherence, a meta-analysis will be beneficial to statistically quantify the association between health literacy/numeracy and medication adherence. Also, a sub-group analysis can be done considering the varying characteristics of the included studies.

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Appendix A. Newcastle-Ottawa Quality Assessment Scale (NOS) adapted for cross-sectional and cohort studies.

CROSS-SECTIONAL STUDIES
Selection (maximum of 5 stars)
Representativeness of sample
a. Truly representative of the average in the target population*
b. Somewhat representative*
c. Selected group of patients
d. No description of sampling strategy

Sample size
a. Justified and satisfactory*
b. Not justified or described

Non-respondents
a. Comparability can be checked if there is no significant difference in the characteristics between respondents and non-respondents, and if response rate is high (≥ 60%) *
b. Response rate is low (< 60%) or the comparability between respondents and non-respondents is unsatisfactory.
c. No description of the response rate or the characteristics of the responders and non-responders

Ascertainment of exposure (Health literacy and/or numeracy)
a. Used a validated measurement tool**
b. Non-validated measurement tool, but tool is available or described*
c. No description of measurement tool

Comparability (maximum 2 stars)
The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
a. The study controls for the most important factor (controls for **age and education level**). *
b. The study control for any additional factor. *

Outcome (maximum 3 stars)
Assessment of the outcome (medication adherence)
a. Record linkage (counting of pills/refill) +/– self-report**
b. Self-report*
c. No description

Statistical Test
a. The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented as either an OR, CI and P value or a beta coefficient, SE and P value. *
b. The statistical test is not appropriate, not described or incomplete.

COHORT STUDIES
Selection (maximum of 5 stars)
Representativeness of exposed cohort
a. Truly representative of the average in the target population*
b. Somewhat representative*
c. Selected group of patients
d. No description of sampling strategy

Selection of the non-exposed cohort from the same source as exposed cohort
a. Yes*
b. No

Ascertainment of exposure
a. Used a validated measurement tool**
b. Non-validated measurement tool, but tool is available or described*
c. No description of measurement tool

Demonstration that outcome of interest was not present at start of study
a. Yes*
b. No

Comparability (maximum 2 stars)
The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
a. The study controls for the most important factor (controls for age and education level). *
b. The study control for any additional factor. *

Outcome (maximum 3 stars)

Assessment of the outcome (medication adherence)

a. Record linkage (counting of pills/refill) +/– self-report**
b. Self-report*
c. No description

Was follow-up long enough for outcomes to occur (≥ 6 months)

a. Yes*
b. No

Adequacy of follow-up of cohorts

a. Complete follow-up – all subjects accounted for *
b. Subjects lost to follow-up unlikely to introduce bias – small number lost (<20%) or attrition described and accounted for in analysis *
c. Follow up rate not adequate and no description of those lost

Good quality: 3, 4 or 5 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain