BMJ Open

Self-reported health literacy and medication adherence in older adults: A systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-056307
Article Type:	Original research
Date Submitted by the Author:	26-Aug-2021
Complete List of Authors:	Schönfeld, Moritz; University Medical Center Hamburg-Eppendorf, Department of Medical Psychology Pfisterer-Heise, Stefanie; University Medical Center Hamburg-Eppendorf, Department of Biochemistry and Molecular Cell Biology Bergelt, Corinna; University Medical Center Hamburg-Eppendorf, Department of Medical Psychology; University Medicine Greifswald, Institute of Medical Psychology
Keywords:	PUBLIC HEALTH, GERIATRIC MEDICINE, STATISTICS & RESEARCH METHODS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Self-reported health literacy and medication adherence in older adults: A systematic review

Schönfeld MS[1], Pfisterer-Heise S[2], Bergelt C[1,3]

[1] Department of Medical Psychology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2] Department of Biochemistry and Molecular Cell Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[3] Department of Medical Psychology, University Medicine Greifswald, Greifswald, Germany

Corresponding author:
Moritz Sebastian Schönfeld
University Medical Center Hamburg-Eppendorf
Department of Medical Psychology
Martinistraße 52
20246 Hamburg
Germany
mo.schoenfeld@uke.de
Tel: +49-40-7410-59140

Word count
5340 words

Date and version
First submission of manuscript: October 29, 2020
1. Resubmission of revised manuscript: August 10, 2021
2. Resubmission of revised manuscript: August 26, 2021

Abstract

Objectives. To explore the associations between self-reported health literacy and medication adherence in older adults.

Design A systematic literature review of quantitative studies published in English and German.

Data sources. MEDLINE via Pubmed, CINAHL, Cochrane Library, Epistemonikos, and LIVIVO were searched.

Eligibility criteria. Included studies had to examine the associations between self-reported health literacy and medication adherence in the elderly (samples with at least 66% of ≥60 years old), had to use a quantitative methodology and had to be written in English or German.

Data extraction and synthesis. All studies were screened for inclusion criteria by two independent reviewers. Data from eligible studies was extracted with the help of a checklist. A narrative synthesis was applied to analyse the studies thematically. Quality assessment was conducted using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI).

Results. We found 2,313 studies of which nine publications from eight studies were included in this review. Five studies reported a majority of participants with limited health literacy, one study reported a majority of participants with adequate health literacy, and three publications from two studies only reported mean levels of health literacy in the elderly. Eight publications from seven studies used self-reports to measure medication adherence. Overall, six publications from five studies reported significantly positive associations between health literacy and medication adherence while two studies reported positive but nonsignificant associations between both constructs and one study reported mixed results.

Conclusion. In this review, associations between self-reported health literacy and medication adherence are rather consistent indicating positive associations between self-reported health literacy and medication adherence in older adults. However, concepts and measures of health literacy and medication adherence applied in the included studies still show a noteworthy amount of heterogeneity. Accordingly, these results reveal the need for more differentiated research on self-reported health literacy and medication adherence in the elderly.

PROSPERO registration number. CRD42019141028.

Strengths and limitations of this study

- To our knowledge, this is the first systematic review to specifically examine existing literature on the association between self-reported health literacy and medication adherence in older adults.
- The review protocol was registered prospectively, and the review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
- Overall, the included studies showed a considerable level of heterogeneity, and the quality of the included studies was predominantly fair, which is a limitation of this review.
- Health literacy is still commonly assessed with performance-based measures, making literature searches for self-reports in this field challenging.

INTRODUCTION

Within the last decades, demographic change and increasing life expectancy have put older adults (≥60 years old as defined by the United Nations[1]) in the focus of health care research. With increasing age, the risk of chronic diseases and comorbidities rises resulting in a growing number of necessary treatments (e.g. medication), and adherence to these treatments becomes crucial to reduce adverse reactions and ensure safe and effective care. In this context, health literacy (HL), often defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions"[2], has been identified as a key influencing factor of improving health-related behaviour in the elderly[3]. Accordingly, (elderly) people with low levels of HL use health care more often and show higher rates of hospitalization than those with high levels of HL[3 4].

Research also confirmed low HL as a predictor of poor health outcomes linking lower HL to higher age[5 6], lower income[5] and lower education[3 7]. In addition, HL has been repeatedly linked to medication adherence, commonly defined as "the extent to which a patient's behaviour corresponds with the prescribed medication dosing regime, including time, dosing and interval of medication intake"[8]. Medication adherence (MA) has been the focus of this research since the number of medications taken commonly increases with increasing age, making medication the most common form of therapy in the elderly, often resulting in polypharmacy[9 10]. Thus, MA still plays a crucial role in the elderly patient´s care. However, research into the associations between HL and MA stays inconclusive[11-16]. While multiple studies reported (significantly) positive associations between HL and MA[17-21], others reported (significantly) negative associations[22 23].

Systematic reviews specifically conducted to analyse the relationship between HL and MA in the elderly resulted in mixed findings as they often included studies with a variety of populations and measures of HL[12 16 24]. Older adults have commonly been examined as a homogenous group not taking into account possible differences in levels of HL and MA between subgroups of age (e.g. 65-70 years old, 71-75 years old, 76-80 years old, 85+ years old[6 25]). In addition, reviews and meta-analyses examining the associations between HL and MA in older age commonly included samples with a wide age range only focusing on the mean age of samples. Since these samples often include (undisclosed) proportions of younger adults and subgroups are not reported, results may not adequately reflect the relationship between HL and MA in older adults[24 26]. Also, reviews commonly included a low proportion of studies measuring HL with self-reports. Instead, many reviews focused on the so-called legacy instruments of HL (i.e. REALM[27], TOFHLA[28])[12 24] including different measures and concepts of HL, which may lead to unknown bias[15 26]. As recently stated by Nguyen *et al*.[29], these often-deployed legacy tools may measure different aspects of literacy and may not be appropriate to assess HL in older adults. Accordingly, limited HL was found to be strongly associated with older age when measured with the TOFHLA (mainly assessing reading, comprehension and numeracy skills[28]) while limited HL had weak associations with older age[30] when measured with the REALM (mainly assessing medical vocabulary[27]).

As of late, these methodological shortcomings in research into HL have been increasingly recognized leading to a broader discussion about the conceptualization and measurement of HL. Most recently, researchers started concentrating on self-report measures of HL as new questionnaires from more comprehensive concepts were developed (e.g. HLS-EU-Q[31]). Compared to performance-based measures, self-reports of HL commonly offer a fast, easy, and inexpensive way to collect data and have a lower risk of stigma[32]. Accordingly, self-reports present important advantages when assessing HL in different populations and contexts as they can be applied more effortless. More recently, some studies began to

investigate levels of HL in different subgroups of older age resulting in a renewed call for more differentiated methods and analyses in this population[25 33].

Thus, our review aims to systematically review the evidence on self-reported HL and MA in older adults (≥60 years old) including: 1. the levels of self-reported HL and MA (if available, levels of different subgroups); 2. the associations between self-reported HL and MA; 3. how self-reported HL and MA are measured; and (if available) 4. moderator and mediator effects of other psychosocial factors.

METHODS

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[34]. A checklist of PRISMA items can be found in online supplementary file S1. This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42019141028. The protocol is presented in online supplementary file S2. Answers to reviewer comments are presented in online supplementary file S3.

Eligibility criteria

Population. Studies examining elderly adults aged 60 years and older were included. In case of study samples with a wider age range, only studies with ≥66% of participants 60 years and older were included to ensure only including studies with a majority of older adults.

Intervention. No specific interventions were included in the criteria. Nevertheless, only studies that assessed associations (e.g. correlation, effect size) between self-reported HL and MA were deemed eligible. Studies that assessed HL solely with a performance-based test instrument (e.g. REALM[27], TOFHLA[28]) were excluded from this review.

Outcomes. Studies examining HL with a validated self-report (subjective measure) as well as MA (measured by e.g. questionnaires, refill records) were included.

Study design. Only primary quantitative research (RCTs, prospective and retrospective cohort studies, and cross-sectional studies) published in English or German was included. In case of multiple time-points, only baseline data was included to ensure comparability.

Data sources and search strategy

An electronic search was performed in five electronic databases (MEDLINE via PubMed (1984-2021), CINAHL (1995-2021), Cochrane Library (1997-2021), Epistemonikos (1995-2021), LIVIVO (1966-2021)) between July 15 and July 30, 2019 by the first author and updated again in July 2021. The search was not limited to a specific time frame. A comprehensive search strategy was applied using combinations of the following search terms: “Health literacy", “illiteracy”, “treatment adherence and compliance”, “patient compliance”, “compliance”, “patient adherence” “adherence”, “non-adherence”, “nonadherence”, “medication adherence”, “discontinuation”, “non-compliance”, “noncompliance”, “termination”, “refill”, "aged”, “old”, “older”, “elderly”, “geriatric”, “oldest”, “elders”. As these databases use partially different search algorithms, the search strategy was adapted using MeSH-Terms and Boolean operators (“AND”, “OR”) if applicable (online supplementary table S1). Although this systematic review focuses on self-reports of HL, the terms “self-report” or “subjective” were not included for reasons of higher sensitivity.

In addition, reference lists from eligible articles were hand searched accordingly. All references were subsequently imported into Endnote X8 reference management software for screening purposes.

Study selection and screening

After removal of duplicates, two raters (MSS, SPH) screened titles and abstracts of all remaining studies for eligibility. A checklist was developed for this purpose. As many studies include HL only as a secondary outcome and may thus not state it in the study's title or abstract, title/ abstract screening was conducted more liberal. Accordingly, two raters (MSS, SPH) assessed the full texts of all previously screened studies independently. Figure 1 shows reasons for study exclusion. In case of discrepancies, conflicts were discussed until consensus was reached.

Quality assessment

The methodological quality of all studies included in this review was assessed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, NIH[35]). Since only baseline data from quantitative research was included, the NHLBI was deemed appropriate. The NHLBI contains 14 criteria mainly to assess the internal validity of a study. Each item was answered "yes" (if criterion was met), "no" (if criterion was not met) or "cannot determine/ not applicable/ not reported". As the NHLBI is not meant to assess the study quality by simply summing up its scores, an overall quality rating ("good", "fair", "poor") for each study included a comprehensive and critical appraisal of each criterion as well as the study as a whole.

Data extraction and synthesis

All relevant data was extracted by the first author with the help of a data extraction checklist containing the following information: title, authors, year published, study design and setting, sample size, age groups, definition and assessment of HL and MA, moderator and mediator effects (if available), statistical measures to calculate associations between HL and MA, statistical significance if available.

As the studies showed heterogeneity due to differences in study design, participants, risk of bias, and operationalization of HL and MA, a narrative synthesis was applied to analyse the studies thematically.

Patient and public involvement

Patients or the public were not involved in this study.

RESULTS

Search results

The literature search resulted in a total of 2,313 studies after removal of duplicates. After screening for title and abstract another 1,769 studies were excluded based on exclusion criteria. Full texts of 544 studies were screened and nine publications from eight studies met all eligibility criteria and were thus included in this review (figure 1). Further details and reasons of exclusion are depicted in figure 1. The main reason for study exclusion in the screening process was lack of self-reports of HL.

Study characteristics

Overall study characteristics are presented in table 1. All included publications were published between 2013 and 2020 with sample sizes between n=116 and n=12,159 (Median=293). The proportion of female participants ranged from 33% to 100% (Median=53.6%). All studies adopted a cross-sectional design (5 survey studies). Three studies (four publications) were conducted in South Korea, and one study each in China, USA, Pakistan, Israel, and Thailand. Studies were conducted across settings of tertiary care hospitals (n=5), primary health care (n=1), private health care centres (n=1), community health care centres (n=1), and clinics (n=1). All studies examined patients/adults with different types of (chronic) diseases: hypertension (n=2), heart diseases (n=1), atrial fibrillation (n=2), osteoporosis (n=1), several chronic diseases (n=3). Due to eligibility criteria restricting included samples to those with ≥66% of older adults (60 years of age and older), all studies focused on the elderly and only two studies also included patients younger than 60 years (table 1). Five studies included samples with a higher proportion of women.

Risk of bias

Study quality in terms of risk of bias was considered poor for one publication and fair for eight publications (online supplementary table S2). In most cases, risk of bias occurred from lack of randomization, blinding, and longitudinal data.

Health literacy – key findings

In five publications from four studies[36-40] self-reported HL was measured using a selection of questions from the Brief Health Literacy Screen (BHLS[41]). The BHLS employs three to fifteen questions (e.g. "How often do you have someone help you read hospital materials?") to identify people with inadequate levels of HL. Another study[42] used the short version of the European Health Literacy Survey Questionnaire (HLS-EU-Q) which was designed by the HLS-EU-Consortium based on a conceptual framework of HL[31]. One study assessed HL with the Single Item Literacy Screener (SILS), which asks ""How often do you need to have someone help when you read instructions, pamphlets, or other written material from your doctor or pharmacy?"[43]. Another two studies adopted the Functional, Communicative, and Critical Health Literacy questionnaire (FCCHL) developed by Ishikawa *et al.*[44], a validated questionnaire that assesses three areas of HL: functional HL, communicative HL, and critical HL.

Results on the overall levels of HL were mixed, yet a tendency towards limited HL (i.e. marginal, low, inadequate) in the elderly was observable. While three publications from two studies[36 37 40] only reported mean levels of HL in samples patients aged 65 years and older, six studies reported different levels of HL (e.g. marginal, low, or adequate HL). Three of these six studies[39 42 45] used cut-offs recommended by the original authors of the assessment instruments whereas three studies[38 46 47] did not report how they calculated HL scores. Five of these six studies[39 42 45-47] found that a majority of the respective samples reported limited HL levels (i.e. more people had low scores of HL; range from 62.6% to 92.5%, Median=74.5%) whereas one study[38] found that a majority of the sample reported adequate levels of HL (i.e. more people had high scores of HL; 76.9%).

Medication adherence – key findings

Four publications from three studies[36 37 40 45] employed versions of the Morisky Medication Adherence Scale (MMAS[48]) to assess MA. The MMAS consists of four to eight questions asking about different aspects of medication intake behaviour (e.g. "Do you sometimes forget to take your medication?"[48]). One study[42]

used the Medical Outcomes Study Specific Adherence Scale (MOS-SAS[49]) which addresses MA ("How often have you done each of the following in the past 4 weeks: Took medication as prescribed (on time without skipping dosis)?") as well as heart-healthy lifestyle behaviour (i.e. six preventive behaviours for coronary heart disease, e.g. low-salt diet). One study[39] used a single-item adopted from Wu *et al*.[50] to assess MA ("In the past week, have you forgotten to take your antithrombotic medication for various reasons?"). Another study[38] adopted three questions from the Coronary Artery Risk Development in Young Adults (CARDIA[51]) to assess MA (1. "In the past month, how often did you take your medications as the doctor prescribed?"; 2. "In the past month, how often did you forget to take 1 or more of your prescribed medications?"; 3. "In the past month, how often did you forget to take 1 or more of your prescribed medications?"). MA was also assessed by the Medication Possession Ratio (MPR) in one study[46]. The MPR commonly represents the period during which a patient has an adequate amount of supply of his/her medication available over a predefined amount of time (e.g. a year). One study assessed MA with the Adherence to Refills and Medication Scale (ARMS[52]) which assesses if a patient can correctly take and refill his or her medication on schedule.

Overall, five publications from four studies[36 37 39 45 46] found that a majority of the sample reported low levels of MA (i.e. more non-adherers; range from 50.2% to 69.4%, Median=59.0%) while three studies[38 42 47] in contrast, found that a majority of the sample reported high levels of MA (i.e. more adherers; range from 84.7% to 98.3%, Median=93.7%). One study reported a sample mean score of MA only[40].

Table 1. Overall summary of included studies

Authors, year	Setting, country	Sample					Risk of bias[1]
		N	Age (years), mean (±SD)	% Female	Age subgroups	Disease	
Lee *et al.*, 2013[36]	Tertiary care hospitals, South Korea	n=293	65+ M=74.4 (6.3)	46.8%	NA	Chronic Diseases	fair
Lee *et al.*, 2017[37]	Tertiary care hospital, South Korea	n=291	65+ M=NA	53.6%	65-74 (57.0%) ≥75 (43.0%)	Chronic Diseases	fair
Lu *et al.*, 2019[42]	Tertiary care hospital, China	n=598	M=65.8 (9.4)	33.3%	≤60 (21.5%) 61-70 (43.0%) 71-80 (29.7%) ≥81 (5.7%)	Coronary Heart Disease	fair
Reading *et al.*, 2019[38]	Private care centres, USA	n=12159	21+ 72.7 (64.4-79.9†, adherent patients) 70.1 (59.5-79.1†, nonadherent patients)	43.0%	<65 (27.2%) 65-74 (30.8%) 75-84 (30.5%) ≥85 (11.5%)	Atrial Fibrillation	poor
Saqlain *et al.*, 2019[45]	Tertiary care centres, Pakistan	n=262	65+ M=NA	64.5%	65-75 (84.7%) 76-85 (11.1%) >85 (4.2%)	Hypertension	fair
Seong *et al.*, 2019[39]	Tertiary general hospital, South Korea	n=277	65+ M=74.2 (7.2)	40.8%	65-70 (32.1%) 70-79 (45.5%) ≥80 (22.4%)	Atrial Fibrillation	fair
Shehadeh-Sheeny *et al.*, 2013[46]	Clinics, Israel	n=303	60+ M=71 (6.04)	100%	60-65 (21.5%) 66-75 (54.1%) 76-85 (24.4%)	Osteoporosis	fair
Song & Park, 2020[40]	Community Health Centre, South Korea	n=116	65+ M=72.7 (6.1)	69.8%	65-69 (38.8%) 70-79 (43.1%) ≥80 (18.1%)	Chronic Diseases	fair
Wannasirikul *et al.*, 2016[47]	Primary Care Centre, Thailand	n=600	60-70 M=65.3 (NA)	75.8%	60-65 (52.7%) 66-70 (47.3%)	Hypertension	fair

Notes and abbreviations. † Median (Interquartile range).[1] Risk of Bias was measured using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, NIH[35]). NA: Not available/ not reported.

Age subgroups – key findings

Seven studies[37-40 42 45 46] included in this review examined age subgroups for differences in HL and/or MA. All of these studies conducted subgroup analyses for differences in MA while only one of these studies[42] examined differences in HL between age subgroups (e.g. 65-75 years old, 76-85 years old, >85 years old; table 2).

Overall, four studies[37 42 45 46] found no significant differences in MA between age subgroups while one study[38] reported age as a significant predictor of medication nonadherence as younger patients (<65 years old) were more likely to be nonadherent compared to old/older patients (age groups 65-74 years old and 75-84 years old) but not compared to the oldest (≥85 years old). One study[40] reported higher MA in 65-69-year-old adults compared to 70-79-year-old adults and ≥80-year-old adults. Another study[39] reported significant differences in adherence levels between age subgroups but did not confirm age as a significant predictor of medication nonadherence in multivariate analyses. Age was significantly associated with HL in one study[42] as patients with limited HL were significantly older compared to those with adequate HL. However, regression analyses did not confirm age as a predictor of limited HL (table 2).

Table 2. Results of age subgroup analyses on associations between age and health literacy, and age and medication adherence.

Authors, year	Age subgroups reported	Age subgroup analyses
Lee *et al.*, 2013[36]	NA	None conducted
Lee *et al.*, 2017[37]	65-74 (57.0%) ≥75 (43.0%)	No significant differences in MA between age groups (χ^2=0.391, p=0.835)
Lu *et al.*, 2019[42]	≤60 (21.5%) 61-70 (43.0%) 71-80 (29.7%) >81 (5.7%)	Patients with limited HL were significantly older than those with adequate HL (p<0.05) Age was not a significant predictor for limited HL in ≥81-year-old patients compared to - patients ≤60 years old (AOR (95% CI) = 0.64 (0.24-1.72), p=0.380) - patients 61-70 years old (AOR (95% CI) = 1.19 (0.49-2.88), p=0.694) - patients 71-80 years old (AOR (95% CI) = 0.97 (0.40-2.40), p=0.955) Age was not a significant predictor for medication nonadherence in ≥81-year-old patients compared to - patients ≤60 years old (AOR (95% CI) = 0.67 (0.19-2.36), p=0.534) - patients 61-70 years old (AOR (95% CI) = 1.43 (0.49-4.17), p=0.518) - patients 71-80 years old (AOR (95% CI) = 1.02 (0.34-3.09), p=0.970)
Reading *et al.*, 2019[38]	<65 (27.2%) 65-74 (30.8%) 75-84 (30.5%) ≥85 (11.5%)	Nonadherence to medication significantly differed according to age (p<0.001) Age was a significant predictor for nonadherence to medication in <65-year-old patients compared to - patients 65-74 years old (AOR (95% CI) = 0.68 (0.55-0.83), p<0.001) - patients 75-84 years old (AOR (95% CI) = 0.67 (0.53-0.84), p<0.001) Age was a not significant predictor for nonadherence to medication in <65-year-old patients compared to - patients ≥85 years old (AOR (95% CI) = 0.86 (0.64-1.16), n.s.)
Saqlain *et*	65-75 (84.7%)	No significant differences in MA between age groups (χ^2=1.631, p=0.442)

al., 2019[45]	76-85 (11.1%) >85 (4.2%)	
Seong *et al*., 2019[39]	65-70 (32.1%) 70-79 (45.5%) ≥80 (22.4%)	Adherence to medication significantly differed with respect to age (χ^2=15.15, p<0.001) Age was a significant predictor for nonadherence to medication in ≥80-year-old patients (univariate regression) compared to - patients ≤79 years old (OR (95% CI) = 2.33 (1.291-4.207), p=0.005, univariate) Age was not a significant predictor for nonadherence to medication in ≥80-year-old patients (multivariate regression) compared to - patients ≤79 years old (OR (95% CI) = 1.24 (0.621-2.459), p=0.546, multivariate)
Shehadeh-Sheeny *et al*., 2013[46]	60-65 (21.5%) 66-75 (54.1%) 76-85 (24.4%)	No significant differences in MA between age groups (p=0.23)
Song & Park, 2020[40]	65-69 (38.8%) 70-79 (43.1%) ≥80 (18.1%)	Adherence to medication significantly differed with respect to age (Z=8.37, p<0.001). Post hoc analysis showed higher MA in 65-69-year-old adults (M=5.1 (2.3)) compared to 70-79 (M=4.0 (2.0)) and ≥80-year-old adults (M=3.0 (1.9)), respectively.
Wannasirikul *et al*., 2016[47]	60-65 (52.7%) 66-70 (47.3%)	None conducted

Notes: NA: Not available/ not reported.

Associations between health literacy and medication adherence

Results of the analyses on associations between HL and MA are depicted in table 3. In addition, an overview of cutoffs and categories used for the measures of HL and MA in the included studies are depicted in online supplementary table S3. All studies conducted analyses on these associations. Overall, six publications from five studies[36-38 40 45 47] reported positive and statistically significant associations between HL and MA while two studies[42 46] did not find any significant associations, and one study[39] reported mixed findings. In detail, one of two publications[36] from one study confirmed HL as the strongest predictor for MA in a hierarchical regression analysis while another publication[36] from this study found significantly positive associations between HL and MA but reported self-efficacy to be the strongest predictor for HL in their support vector machine (SVM) model. Another study[42] found no significant differences between limited compared to adequate HL in (medication) nonadherent patients with coronary heart disease. However, the study reported that patients with limited HL were more likely to be nonadherent to secondary adherence measures (i.e. heart-healthy lifestyle, alcohol intake control, exercise, stress management) and suggested that changing how to take your pills may be easier than changing lifestyle behavior. In a study among ethnically diverse patients with atrial fibrillation[38], patients with inadequate levels of HL were significantly more likely to be nonadherent to medication than those with adequate levels of HL. In addition, the study found that included patients with self-reported physical inactivity (vs. physical activity), alcohol use (vs. no alcohol use), and diabetes mellitus were more likely to be nonadherent to medication, whereas patients with diagnosis of hypertension were less likely to be nonadherent to medication. A study on outpatients with hypertension[45] found positive and statistically

significant associations between HL and MA as well as a higher likelihood of patients with adequate levels of HL to be adherent to medication compared to patients with inadequate levels of HL. In their multivariate logistic regression, the same study found that in addition to adequate HL, self-reported good and moderate subjective health as well as independence in activities of daily living were also independent predictors of MA in the elderly. Another study[39] reported significant differences in adherence to antithrombotic medication by levels of HL but did not confirm HL as a significant predictor for MA in older adults. They concluded that a significant association between HL and MA might exist still since in their univariate regression the rate of inadequate HL was higher in the group of nonadherent patients compared to adherent patients. However, in their multivariate logistic regression, the authors[39] found only cognitive impairment to be a significant predictor of medication nonadherence in older patients with atrial fibrillation. One study[46] found no significant association between HL and MA in a population of female Arab osteoporosis patients and found only self-reported income to be a significant predictor of adherence in the conducted multivariate logistic regression. Another study[40] found significantly positive associations between HL and MA. In their multiple regression analysis, the authors also found that income, number of chronic diseases, vision problems, and HL were significant predictors of MA. One other study[47] analysed the relationship between HL, MA, and blood pressure levels in primary care patients with hypertension using a Structural Equation Modeling (SEM) approach, which supported the existence of a causal relationship between these factors. Accordingly, HL had a positive but small statistically significant direct effect on MA. Literacy and cognitive ability had the biggest direct effects on both HL and MA. Additionally, HL had the biggest significantly negative direct effect on blood pressure levels (i.e. the higher the HL, the lower the blood pressure level). Based on the SEM, the authors of this study[47] suggested a mediator effect of HL on MA, even though no analysis was conducted. None of the other studies performed mediator and/or moderator analyses concerning HL and/or MA and other factors

300

Table 3. Detailed analyses of health literacy and medication adherence

Authors, year	Sample and setting	HL measures	MA measure	Key results	Associations between HL and MA and further outcomes
Lee *et al.*, 2013[36]	n=293, 65+ years M=74.4 years (6.3) Patients with chronic diseases from tertiary care hospitals in Cheonan, South Korea	BHLS 3 questions	MMAS-4	Mean HL was 8.3 (1.9) n=120 (41.0%) patients were adherent to medication	Significant associations between HL and MA (p=NA) Self-efficacy was strongest predictor for MA in SVM model Other factors significantly associated with MA were number of medication types, daily pill counts, duration after diagnosis
Lee *et al.*, 2017[37]	n=291, 65+ years M=NA Patients with chronic diseases from tertiary care hospital in South Korea	BHLS 15 questions	MMAS-8	Mean HL was 46.61 (12.66) n=89 (30.6%) patients were highly adherent with MMAS-Score of 8 Mean MA was at a medium level (M=6.32 (1.61))	HL positively correlated with MA (r=0.25, p<0.001) HL was strongest predictor of MA in hierarchical linear regression (β=0.190, p<0.001) Other significant predictors of MA in regression were perceived health status (β=0.132, p<0.02), use of magnifying glass (β=0.166, p<0.003), assistance with medication administration (β=0.120, p<0.035)
Lu *et al.*, 2019[42]	n=598 M=65.8 years (9.4) Patients with coronary heart disease from tertiary hospital in Shanghai, China	HLS-EU-Q16	MOS-SAS	HL was limited for n=444 (74.5%) and adequate for n=152 (25.5%) patients Patients with limited HL were significantly older than those with adequate HL (p=0.003) n=505 (84.7%) patients were adherent to medication	No significant associations between HL and MA (χ^2=NA, p=0.125) No significant predictive relationship between limited HL and medication nonadherence (AOR (95% CI) = 0.66 (0.39-1.11), p=0.113) Patients with limited HL compared to those with adequate HL were more likely to be nonadherent to overall heart-healthy lifestyle behaviour (AOR (95% CI) = 1.69 (1.13-2.53), p=0.010), exercise (AOR (95% CI) = 1.50 (1.01-2.22), p=0.046), alcohol intake control (AOR (95% CI) = 2.19 (1.21- 3.96), p=0.010), and stress management (AOR (95% CI) = 2.09 (1.32-3.29), p=0.002)
Reading *et al.*, 2019[38]	n=12159, 21+ years Age median was 72.7 and 70.1 years for adherent and nonadherent patients, respectively Ethnically diverse patients with atrial fibrillation from Northern California, USA	BHLS 3 questions	CARDIA (3 questions)	n=9349 (76,9%) patients had adequate HL n=771 (6.3%) patients were nonadherent to medication Significant differences in MA between age subgroups (p<0.001)	Patients with inadequate HL were more likely to be nonadherent to medication compared to those with adequate HL (AOR (95% CI) = 1.32 (1.09-1.60), p<0.01) in multivariate logistic regression model Patients were more likely to be nonadherent to medication if physically inactive (AOR (95% CI) = 1.57 (1.16-2.13), p<0.01), drinking alcohol (AOR (95% CI) = 1.91 (1.51-2.43), p<0.001), having diagnosis of diabetes mellitus (AOR (95% CI) = 1.22 (1.01-1.48), p<0.05), having 1-7 days of self-reported poor physical health (AOR (95% CI) = 1.43 (1.17-1.75), p<0.001) Patients were less likely to be nonadherent to medication if having diagnosis of hypertension (AOR (95% CI) = 0.72 (0.60-0.87), p<0.05), age between 65-74 (AOR (95% CI) = 0.68 (0.55-0.83), p<0.001) and age between 75-84 (AOR (95% CI) = 0.67 (0.53-0.84), p<0.001)

Saqlain *et al*., 2019[45]	n=262, 65+ years M=NA Outpatients with hypertension from tertiary health care centres in Islamabad, Pakistan	SILS	MMAS-4	n=98 (37.4%) patients had adequate HL n=102 (38.9%) patients were adherent to medication	Positive and statistically significant associations between HL and MA (χ^2=24.356, p<0.001) Patients with adequate HL were more likely to be adherent to medication compared to those with inadequate HL (OR (95% CI) = 3.37 (1.91-5.96), p<0.001) Other significant predictors of MA were self-reported good (OR (95% CI) = 4.25 (1.45-12.44), p<0.008) and moderate (OR (95% CI) = 3.54 (1.37-9.16), p<0.009) subjective health and independence in activities of daily living (OR (95% CI) = 2.97 (1.15-5.85), p<0.002)
Seong *et al*., 2019[39]	n=277, 65+ years M=74.2 (7.2) Outpatients with atrial fibrillation undergoing antithrombotic therapy in tertiary general hospital in South Korea	BHLS 3 questions	Single item ("In the past week, have you forgotten to take your antithrombotic medication for various reasons?")	HL levels (M=7.9 (3.5)) were inadequate, marginal, and adequate for 28.1%, 45.5%, and 26.4% of patients, respectively n=139 (50.2%) patients were nonadherent to medication Significant differences in MA between age subgroups (p<0.001)	Positive and statistically significant associations between HL and MA (χ^2=22.00, p<0.001) Significant predictive relationship between marginal/ inadequate HL and medication nonadherence in univariate logistic regression analysis (OR (95% CI) = 2.55 (1.29-3.90), p=0.004) but not in multivariate logistic regression analysis (OR (95% CI) = 1.45 (0.79-2.64), p=0.232), where only cognitive impairment was significant predictor for medication nonadherence (OR (95% CI) = 2.63 (1.42-4.85), p=0.002)
Shehadeh-Sheeny *et al*., 2013[46]	n=303, 60+ years M= 71 (6.04) Female Arab patients with osteoporosis from three clinics in Israel	FCCHL	MPR	n=75 (24.8%) patients had high HL compared to n=164 (54.1%) and n=64 (21.1%) with medium and low HL, respectively n=125 (41.3%) patients had high MA	No significant associations between MA and HL (p=0.44) 46.7% of patients with high HL were more adherent to medication compared to 35.9% of patients with low HL In multivariate logistic regression only self-reported income was a significant predictor of MA (OR (95% CI) = 1.26 (1.01-1.58), p=0.037)
Song & Park, 2020[40]	n=116, 65+ years M=72.7 (6.1) Community-dwelling older adults in health care centre, South Korea	BHLS 15 questions	MMAS-8	Mean HL was 42.4 (6.6) Mean MA was at a medium level (M=4.3 (2.2))	HL positively correlated with MA (r=0.42, p<0.001) In multiple regression analysis HL was significant predictor of MA in multiple regression (β=0.23, p<0.001) Other significant predictors of MA were income (β=0.35, p<0.001), number of chronic diseases (β=-0.33, p<0.001), and vision problems (β=-0.32, p<0.001)

Wannasirikul *et al.*, 2016[47]	n=600, 60-70 years M=65.3 Patients with hypertension from primary health care centre in Sa Kaeo Province, Thailand	FCCHL	ARMS	Mean HL was 40.0 (10.4) HL levels were inadequate, marginal, and adequate for 48.7%, 43.8%, and 7.5% of patients, respectively MA was good for 98.3% of patients	SEM supports causal relationship between HL, MA, and blood pressure HL had a significantly positive direct effect on MA in SEM (β=0.08, p<0.05) Cognitive ability ((β=0.22, p<0.05) and literacy (β=0.46, p<0.05) had biggest and significantly positive direct effect on MA Literacy (β=0.15, p<0.05) and cognitive ability (β=0.52, p<0.05) had biggest and significantly positive direct effect on HL HL had biggest significantly negative direct effect on blood pressure level (β=-0.14, p<0.05) MA had a significantly negative direct effect on blood pressure level (β=--0.02, p<0.05) Results suggest mediator effect of HL on MA

Abbreviations: BHLS: Brief Health Literacy Screen, MMAS: Morisky Medication Adherence Scale, HLS-EU-Q: European HL Survey Questionnaire, MOS-SAS: Medical Outcomes Study Specific Adherence Scale, CARDIA: Coronary Artery Risk Development in Young Adults, SILS: Single Item Literacy Screener, FCCHL: Functional, Communicative, and Critical Health Literacy Questionnaire, MPR: Medication Possession Ratio, ARMS: Adherence to Refills and Medications Scale, NA: Not available/ not reported.

DISCUSSION

The aim of this study was to systematically examine the associations of HL and MA in older adults. Although research on HL and MA in older adults has rapidly increased in the last years, mixed results are a common denominator in this area[15 53]. Accordingly, previous systematic reviews resulted in a range of conclusions as they included a variety of HL concepts, different (younger) age groups, and a range of methodologically different instruments (self-reports as well as performance-based measures) to assess HL[12 16 24 26 53]. To our knowledge, this is the first systematic review to focus specifically on self-reported HL while explicitly including studies with samples of older adults. We found that only few validated instruments of self-reported HL are used and that most studies still rely on legacy measures to assess HL even though their use has been criticized repeatedly and self-reports of HL offer a range of advantages[32]. Studies included in our review mostly assessed MA in older adults through self-reports, even though a wide range of tools is known[54 55].

In this review, results appear to be more consistent in contrast to previous reviews[15 16] as many included studies reported positive and statistically significant associations between HL and MA. This could be explained by the fact that only older adults (at least 66% of older adults in samples, not based on the samples´ mean age) were examined in the included studies and associations in this group may be more prominent compared to studies that also include subgroups of younger people. One review[24] for example aimed to review literature that examined HL and MA in older adults with cardiovascular disease or diabetes. Included studies in the review had to assess HL with legacy instruments only and had to include samples of participants with a "[…] mean age [of] at least 50 years or with at least a third of participants aged 50 years or older […]" and could not confirm an association between HL and MA. As stated earlier, inclusion of younger participants may have resulted in unknown bias from age. Yet another bias may have resulted from the utilization of legacy measures with different conceptualizations of HL since the REALM and TOFHLA, two of the most prominent legacy tools of HL, are confirmed to assess different aspects of literacy rather than HL and may thus be differently impacted by a person´s intelligence[29]. Accordingly, Loke *et al*. stated in their review that functional measures of HL may not be adequate and "[n]ew methods of measuring health literacy beyond the functional level are needed […]".

In another review, Ostini *et al*.[16] included studies with samples of all age groups, not disclosing how HL and MA were measured in these studies, and suggested the existence of a U-shaped relationship between HL and nonadherence as patients with high levels of HL may intentionally not adhere while those with low HL levels may unintentionally not adhere. Looking at the included studies in their review, only one study used a self-report measure of HL (BHLS) while all other used one of the performance-based legacy instruments. Since legacy measures of HL rather focus on literacy skills and we could not find any indication of a U-shaped relationship in our review, we want to point out that, while we cannot confirm or rule out a U-shaped relationship between literacy skills and MA, our review might suggest that it does not exist between self-reported HL and MA in older adults. While people with low literacy skills may not be able to understand/read labels/instructions and therefore not adhere (or rather unintentionally not comply) to their medication more often, people with higher literacy skills might read instructions first and subsequently (intentionally) decide not to take their medications due to e.g. possible side effects they read about. However, this phenomenon is not easily transferrable onto other and in some cases broader theoretical concepts of self-reported HL measures (e.g. HLS-EU-Q) since those not only include literacy skills but also other individual skills and situational aspects and may thus show another linear or non-linear association with adherence. Since empirical data on possible associations between literacy and self-

reported HL are still widely lacking, we need more research to explore and develop comprehensive theories in this area.

Six studies[38 39 42 45-47] included in this review found that a majority of participants in the respective samples reported limited (i.e. inadequate, low, marginal) HL. This is consistent with other research that showed that older people commonly reach only low levels of self-reported health literacy[3 25 33] even though this research is very scarce. HL was measured by versions of four different self-reports (BHLS[41 56], HLS-EU-Q[3], SILS[43], FCCHL[44]). This shows that self-reporting HL measures are still rarely utilized when examining older adults, even though the Health literacy Tool Shed[57] lists 29 self-report instruments for HL in English alone (58 without language restrictions).

MA was assessed through self-reports in all but one of the included studies[36-40 42 45 47]. Nevertheless, we recommend a more detailed description of operationalization of MA as many studies still use the concepts of adherence and compliance interchangeably. Interestingly, we had to exclude many studies from this review even though they assessed some form of adherence, because they only included measures of general preventive behaviour (e.g. physical activity) and not MA. However, the use of such secondary adherence measures might be a promising approach to get a more comprehensive picture of adherence in older adults[55]. Especially a multi-method approach could be helpful since self-reported adherence may also be affected by cognitive bias and/or social desirability in older adults. As such, the utilization of both direct (e.g. laboratory measures) and indirect (e.g. self-reports) measures of adherence[55 58] may help to get a better understanding of adherence and its associations with self-reported HL in older adults. A number of studies in this review also included measures of secondary prevention (e.g. physical activity, heart-healthy lifestyle behavior) as well as other factors (e.g. income, cognitive ability) providing further knowledge on possible confounders in the mechanisms between HL and MA. Accordingly, several studies confirmed multiple other factors as predictors for MA (e.g., health status[37 38 45], income[40 46], physical activity[38 45], cognitive ability[39 47]) and/ or HL (e.g., cognitive ability[47], stress management[42]). In a recent systematic review and meta-analysis by Lim et al.[59], the authors examined the associations between physical activity and HL and found that older adults with inadequate levels of HL were "[…] less likely […] to report engaging in physical activity […]" than those with adequate HL, showing the importance of also addressing secondary adherence measures in future research in this area. Notably, their review also included younger adults (samples with mean age ≥55 years) and different of HL measures (legacy measures and self-reports).

Even though we also encourage researchers to assess HL with a multi-method approach (e.g. subjective and objective instruments), we suggest a more rigorous differentiation in analysis and interpretation when comparing HL measures that are based on different concepts (e.g. legacy tools and self-reports). This may also help to clarify further the associations between self-reported HL and literacy as measured by legacy instruments. As stated by Nguyen *et al*.[29], a separation in analyses of objective and subjective measures of HL as well as a closer alignment of HL theory and measurement could help clarify the relationship between HL and MA. This idea was also supported by one of the studies[40] included in this review, which aimed at comparing two different measures of HL (self-report vs. legacy measure). The authors found that even though both measures were significantly and positively correlated to MA, only the self-report was a significant predictor for MA in older adults suggesting that self-reports may be more fitting to access HL when predicting MA since "[…] assessing older adults´ experiences of limited health literacy is more appropriate for catching any decreased medication adherence […]".

This review additionally confirms that age subgroup analyses are conducted very rarely for self-reported HL but quite often for MA. This may result from the fact that research on MA in the elderly is traditionally older than research on HL in the elderly and with regard to HL most studies still treat older people as a homogenous group[25]. Most studies in this review did not find any significant associations between age and MA and only two studies[38 40] reported significant differences in MA between age subgroups. Accordingly, one study[38] reported that young/ young-old people (21-65 years old) were more likely not to adhere to their medication compared to old/older adults (65-84 years old) but not oldest adults (≥85 years old). A second study[40] reported higher MA in 65-69-year-old adults compared to older/oldest adults (70-90 years old). Not surprisingly, only one study conducted analyses on the relationship between age and HL[42], showing that patients with limited HL were significantly older compared to those with adequate HL. Even though generalizability is very limited, these results reveal the necessity for more differentiated analyses (e.g. of subgroups) in future HL and MA research on older adults. In context of demographic change and increasing life expectancy, more differentiated analyses could help to understand specific needs and barriers of elderly (patient) populations with different chronic diseases. Importantly, definitions of *old age* are often inconsistent and include people from ages 60, 65, or 70 years and over. These dissimilarities in the definitions of old age may result from differences in cultural and/or economic standards (e.g. USA vs. Asia) and often manifest in different demographic changes and/or different life expectancies thus resulting in a different quality of health care in groups of older adults. Consequently, when looking at older adults´ health care and health outcomes, it is critical to include contextual aspects such as cultural or economic standards.

Studies in this review show some inconsistencies in the use of cutoffs, use, and wording of HL levels. Of all included studies, six studies[38 39 42 45-47] reported categories of HL (e.g. adequate) of which only three[39 42 45] reported cutoffs for these categories. Three publications[36 37 40] from two studies reported neither categories nor cutoffs for HL and only five publications[36 37 39 40 47] from four studies reported mean values of HL. For example, Shehadeh-Sheeny et al. calculated scores for low, medium, and high levels of HL while Wannasirikul et al. calculated scores for adequate, marginal, and inadequate HL levels even though no cutoffs were reported/available by neither the authors nor the FCCHL measure both studies used. The inconsistent use of cutoffs and wording may indicate a lack of certainty and experience in the application of self-reports enhancing the call for more differentiated research and the development of easy-to-use but still valid tools.

Strength and limitations

The strengths of this study include the exhaustive methodology and comprehensive search strategy that were used. As we followed a strict screening procedure, we are confident that we found all eligible studies. Since we excluded all studies that measured HL with performance-based instruments, we aimed to reduce bias resulting from fundamental differences in constructs and concepts. Although we see this exclusion as a considerable advantage, we cannot eliminate the possibility of bias still resulting from theoretical or practical differences in self-reports as some of them are built on more complex conceptual frameworks than others. Additionally, there are advantages in assessing HL in older adults with self-reports since they reduce the possible bias of performance-based measures resulting from fear of stigma and/or (time)

pressure. Nevertheless, we recognize the inherent limitations of self-reporting tools that may also have biased our results.

Other limitations should be considered. All studies included in this review were cross-sectional, thus we cannot determine any direction of causality. The fair to poor methodological quality of the included studies may also increase the risk of (unknown) bias. Given the heterogeneity of the studies, a meta-analysis (e.g. pooled odds ratios) could not be conducted, thus limiting further understanding of the relationship between HL and MA in older adults. Additionally, our search strategy in this review limited included studies to English and German, which could bias results due to missing research in other languages. Finally, we were not able to include EMBASE as a database in our search. Even though, we are very confident that we did not miss a substantial amount of literature, this must be considered as a limitation of this review.

CONCLUSIONS

In this review, self-reported HL and MA in older adults show a rather straightforward positive association. While previous research on HL and MA in older adults did not always find clear associations, many studies included in this review reported significantly positive associations between HL and MA. In addition, HL plays an important role as a predictor of MA in older adults as several studies in this review could confirm. However, other factors (e.g. cognitive ability) appear equally important in predicting MA in older adults, and future studies should also focus on secondary adherence measures (e.g. physical activity) when examining the associations between HL and MA in the elderly. Finally, study heterogeneity and methodological weaknesses reveal a definitive need for more differentiated research regarding different definitions, concepts, and measures of HL and MA as well as longitudinal research designs and studies that analyse age subgroups in older adults.

Acknowledgements
We would like to thank Dr. rer. biol. hum. Laura Inhestern for her advice during the preparation of the search for this review.

Author Contributions
All Authors were involved in the design and planning of the review. MSS prepared, performed, and redefined the searches after consultation with SPH and CB. MSS and SPH performed screening and data extraction with the help of CB in case of disagreements or discussion. All authors contributed to the data analysis and interpretation. MSS wrote the first draft which was critically revised by SPH and CB.

Ethics Approval Statement
This study does not involve human participants, as it is a systematic review.

Funding
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests
None declared.

Patient consent
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data sharing statement
All data relevant to the study are included in the article or uploaded as supplementary information.

REFERENCES

1 United Nations DoEaSA, Population Division. World Population Ageing 2019: Highlights (ST/ESA/SER.A/430) 2020.

2 Ratzan SC, Parker RM. Health literacy - identification and response. *J Health Commun* 2006;**11**:713-5.doi:10.1080/10810730601031090

3 HLS-EU Consortium. Comparative Report on Health Literacy in Eight EU Member States. The European Health Literacy Project 2009–2012. Vienna: Ludwig Boltzmann Institute for Health Promotion Research 2012.

4 Berkman ND, Sheridan SL, Donahue KE, et al. Low health literacy and health outcomes: an updated systematic review. *Ann Intern Med* 2011;**155**:97-107.doi:10.7326/0003-4819-155-2-201107190-00005

5 Chesser AK, Keene Woods N, Smothers K, et al. Health Literacy and Older Adults: A Systematic Review. *Gerontol Geriatr Med* 2016;**2**:2333721416630492.doi:10.1177/2333721416630492

6 Vogt D, Schaeffer D, Messer M, et al. Health literacy in old age: results of a German cross-sectional study. *Health Promot Int* 2018;**33**:739-47.doi:10.1093/heapro/dax012

7 Wolf MS, Feinglass J, Thompson J, et al. In search of 'low health literacy': threshold vs. gradient effect of literacy on health status and mortality. *Soc Sci Med* 2010;**70**:1335-41.doi:10.1016/j.socscimed.2009.12.013

8 Gast A, Mathes T. Medication adherence influencing factors—an (updated) overview of systematic reviews. *Systematic Reviews* 2019;**8**:1-17.doi:10.1186/s13643-019-1014-8

9 Hoel RW, Connolly RMG, Takahashi PY. Polypharmacy Management in Older Patients. *Mayo Clinic Proceedings* 2021;**96**:242-56.doi:10.1016/j.mayocp.2020.06.012

10 Chiatti C, Bustacchini S, Furneri G, et al. The economic burden of inappropriate drug prescribing, lack of adherence and compliance, adverse drug events in older people: a systematic review. *Drug Saf* 2012;**35 Suppl 1**:73-87.doi:10.1007/BF03319105

11 Huang YM, Shiyanbola OO, Smith PD. Association of health literacy and medication self-efficacy with medication adherence and diabetes control. *Patient Prefer Adherence* 2018;**12**:793-802.doi:10.2147/PPA.S153312

12 Martins NFF, Abreu DPG, Silva BTD, et al. Functional health literacy and adherence to the medication in older adults: integrative review. *Rev Bras Enferm* 2017;**70**:868-74.doi:10.1590/0034-7167-2016-0625

13 Park NH, Song MS, Shin SY, et al. The effects of medication adherence and health literacy on health-related quality of life in older people with hypertension. *Int J Older People Nurs* 2018;**13**:e12196.doi:10.1111/opn.12196

14 Roh YH, Koh YD, Noh JH, et al. Effect of health literacy on adherence to osteoporosis treatment among patients with distal radius fracture. *Arch Osteoporos* 2017;**12**:42.doi:10.1007/s11657-017-0337-0

15 Zhang NJ, Terry A, McHorney CA. Impact of health literacy on medication adherence: a systematic review and meta-analysis. *Ann Pharmacother* 2014;**48**:741-51.doi:10.1177/1060028014526562

16 Ostini R, Kairuz T. Investigating the association between health literacy and non-adherence. *International journal of clinical pharmacy* 2014;**36**:36-44.doi:10.1007/s11096-013-9895-4

17 Lindquist LA, Go L, Fleisher J, et al. Relationship of health literacy to intentional and unintentional non-adherence of hospital discharge medications. *J Gen Intern Med* 2012;**27**:173-8.doi:10.1007/s11606-011-1886-3

18 Wolf MS, Davis TC, Osborn CY, et al. Literacy, self-efficacy, and HIV medication adherence. *Patient Educ Couns* 2007;**65**:253-60.doi:10.1016/j.pec.2006.08.006

19 Kripalani S, Gatti ME, Jacobson TA. Association of age, health literacy, and medication management strategies with cardiovascular medication adherence. *Patient Educ Couns* 2010;**81**:177-81.doi:10.1016/j.pec.2010.04.030

20 Bauer AM, Schillinger D, Parker MM, et al. Health literacy and antidepressant medication adherence among adults with diabetes: the diabetes study of Northern California (DISTANCE). *J Gen Intern Med* 2013;**28**:1181-7.doi:10.1007/s11606-013-2402-8

21 Mayo-Gamble TL, Mouton C. Examining the Association Between Health Literacy and Medication Adherence Among Older Adults. *Health Commun* 2018;**33**:1124-30.doi:10.1080/10410236.2017.1331311
22 Mosher HJ, Lund BC, Kripalani S, et al. Association of health literacy with medication knowledge, adherence, and adverse drug events among elderly veterans. *J Health Commun* 2012;**17 Suppl 3**:241-51.doi:10.1080/10810730.2012.712611
23 Fang MC, Machtinger EL, Wang F, et al. Health literacy and anticoagulation-related outcomes among patients taking warfarin. *J Gen Intern Med* 2006;**21**:841-6.doi:10.1111/j.1525-1497.2006.00537.x
24 Loke YK, Hinz I, Wang X, et al. Systematic review of consistency between adherence to cardiovascular or diabetes medication and health literacy in older adults. *Ann Pharmacother* 2012;**46**:863-72.doi:10.1345/aph.1Q718
25 Vogt D, Berens EM, Schaeffer D. [Health Literacy in Advanced Age]. *Gesundheitswesen* 2020;**82**:407-12.doi:10.1055/a-0667-8382
26 Geboers B, Brainard JS, Loke YK, et al. The association of health literacy with adherence in older adults, and its role in interventions: a systematic meta-review. *BMC Public Health* 2015;**15**:903.doi:10.1186/s12889-015-2251-y
27 Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened screening instrument. *Fam Med* 1993;**25**:391-5
28 Parker RM, Baker DW, Williams MV, et al. The test of functional health literacy in adults: a new instrument for measuring patients' literacy skills. *J Gen Intern Med* 1995;**10**:537-41.doi:10.1007/BF02640361
29 Nguyen TH, Paasche-Orlow MK, McCormack LA. The State of the Science of Health Literacy Measurement. *Stud Health Technol Inform* 2017;**240**:17-33
30 Kobayashi LC, Wardle J, Wolf MS, et al. Aging and Functional Health Literacy: A Systematic Review and Meta-Analysis. *J Gerontol B Psychol Sci Soc Sci* 2016;**71**:445-57.doi:10.1093/geronb/gbu161
31 Sorensen K, Van den Broucke S, Pelikan JM, et al. Measuring health literacy in populations: illuminating the design and development process of the European Health Literacy Survey Questionnaire (HLS-EU-Q). *BMC Public Health* 2013;**13**:948.doi:10.1186/1471-2458-13-948
32 Nguyen TH, Paasche-Orlow MK, McCormack LA. The state of the science of health literacy measurement. *Information Services & Use* 2017;**37**:189--203.doi:10.3233/isu-170827
33 Berens EM, Vogt D, Messer M, et al. Health literacy among different age groups in Germany: results of a cross-sectional survey. *BMC Public Health* 2016;**16**:1151.doi:10.1186/s12889-016-3810-6
34 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.doi:10.1371/journal.pmed.1000097
35 National Heart, Lung, and Blood Institute. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. 2014. Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort.
36 Lee SK, Kang BY, Kim HG, et al. Predictors of medication adherence in elderly patients with chronic diseases using support vector machine models. *Healthc Inform Res* 2013;**19**:33-41.doi:10.4258/hir.2013.19.1.33
37 Lee YM, Yu HY, You MA, et al. Impact of health literacy on medication adherence in older people with chronic diseases. *Collegian* 2017;**24**:11-8.doi:10.1016/j.colegn.2015.08.003
38 Reading SR, Black MH, Singer DE, et al. Risk factors for medication non-adherence among atrial fibrillation patients. *BMC Cardiovasc Disord* 2019;**19**:38.doi:10.1186/s12872-019-1019-1
39 Seong HJ, Lee K, Kim BH, et al. Cognitive Impairment Is Independently Associated with Non-Adherence to Antithrombotic Therapy in Older Patients with Atrial Fibrillation. *Int J Environ Res Public Health* 2019;**16**.doi:10.3390/ijerph16152698
40 Song MS, Park S. Comparing two health literacy measurements used for assessing older adults' medication adherence. *J Clin Nurs* 2020;**29**:4313-20.doi:10.1111/jocn.15468

41 Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. *Fam Med* 2004;**36**:588-94
42 Lu M, Ma J, Lin Y, et al. Relationship between patient's health literacy and adherence to coronary heart disease secondary prevention measures. *J Clin Nurs* 2019;**28**:2833-43.doi:10.1111/jocn.14865
43 Morris NS, MacLean CD, Chew LD, et al. The Single Item Literacy Screener: evaluation of a brief instrument to identify limited reading ability. *BMC Fam Pract* 2006;**7**:21.doi:10.1186/1471-2296-7-21
44 Ishikawa H, Takeuchi T, Yano E. Measuring functional, communicative, and critical health literacy among diabetic patients. *Diabetes Care* 2008;**31**:874-9.doi:10.2337/dc07-1932
45 Saqlain M, Riaz A, Malik MN, et al. Medication Adherence and Its Association with Health Literacy and Performance in Activities of Daily Livings among Elderly Hypertensive Patients in Islamabad, Pakistan. *Medicina (Kaunas)* 2019;**55**.doi:10.3390/medicina55050163
46 Shehadeh-Sheeny A, Eilat-Tsanani S, Bishara E, et al. Knowledge and health literacy are not associated with osteoporotic medication adherence, however income is, in Arab postmenopausal women. *Patient Educ Couns* 2013;**93**:282-8.doi:10.1016/j.pec.2013.06.014
47 Wannasirikul P, Termsirikulchai L, Sujirarat D, et al. Health Literacy, Medication Adherence, and Blood Pressure Level among Hypertensive Older Adults Treated at Primary Health Care Centers. *Southeast Asian J Trop Med Public Health* 2016;**47**:109-20
48 Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;**24**:67-74.doi:10.1097/00005650-198601000-00007
49 Sherbourne CD, Hays RD, Ordway L, et al. Antecedents of adherence to medical recommendations: results from the Medical Outcomes Study. *J Behav Med* 1992;**15**:447-68.doi:10.1007/BF00844941
50 Wu JR, DeWalt DA, Baker DW, et al. A single-item self-report medication adherence question predicts hospitalisation and death in patients with heart failure. *J Clin Nurs* 2014;**23**:2554-64.doi:10.1111/jocn.12471
51 Cutter GR, Burke GL, Dyer AR, et al. Cardiovascular risk factors in young adults. The CARDIA baseline monograph. *Control Clin Trials* 1991;**12**:1S-77S.doi:10.1016/0197-2456(91)90002-4
52 Kripalani S, Risser J, Gatti ME, et al. Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients with chronic disease. *Value Health* 2009;**12**:118-23.doi:10.1111/j.1524-4733.2008.00400.x
53 Miller TA. Health literacy and adherence to medical treatment in chronic and acute illness: A meta-analysis. *Patient Educ Couns* 2016;**99**:1079-86.doi:10.1016/j.pec.2016.01.020
54 Lam WY, Fresco P. Medication Adherence Measures: An Overview. *Biomed Res Int* 2015;**2015**:217047.doi:10.1155/2015/217047
55 Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment adherence. *Med Pharm Rep* 2019;**92**:117-22.doi:10.15386/mpr-1201
56 Chew LD, Griffin JM, Partin MR, et al. Validation of screening questions for limited health literacy in a large VA outpatient population. *J Gen Intern Med* 2008;**23**:561-6.doi:10.1007/s11606-008-0520-5
57 Health Literacy Tool Shed [Internet]. Boston University, Research Trinagle Institute International. [cited 08/17/2020]. Available from: https://healthliteracy.bu.edu.
58 McRae-Clark AL, Baker NL, Sonne SC, et al. Concordance of Direct and Indirect Measures of Medication Adherence in A Treatment Trial for Cannabis Dependence. *J Subst Abuse Treat* 2015;**57**:70-4.doi:10.1016/j.jsat.2015.05.002
59 Lim ML, van Schooten KS, Radford KA, et al. Association between health literacy and physical activity in older people: a systematic review and meta-analysis. *Health Promot Int* 2020;**daaa072.**doi:10.1093/heapro/daaa072

Figure 1. PRISMA Flow Diagram
Note: *only for samples that not exclusively focus on elders

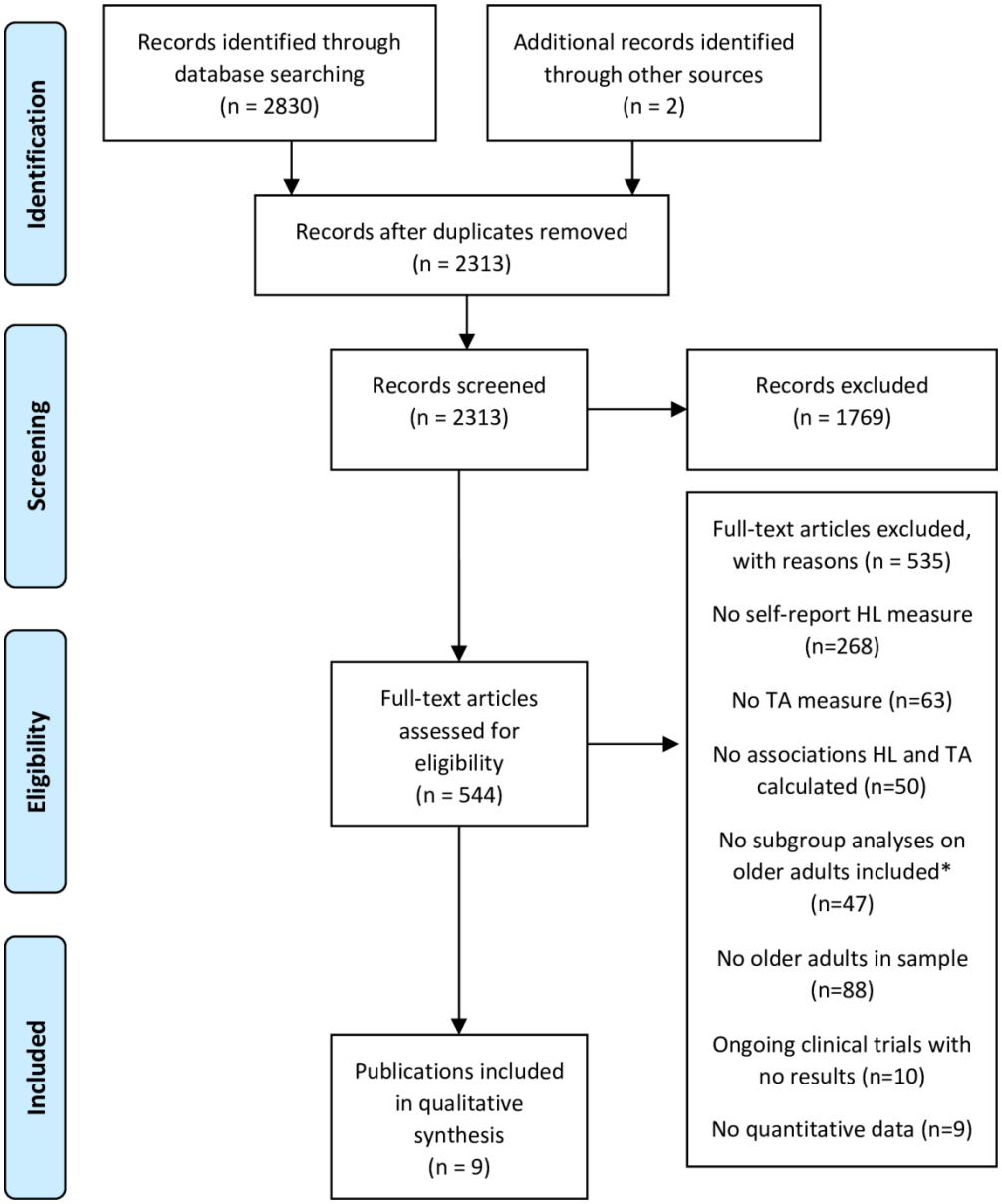

Figure 1. PRISMA Flow Diagram Note: *only for samples that not exclusively focus on elders

129x155mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Citation

Moritz Schoenfeld, Stefanie Pfisterer-Heise, Corinna Bergelt. Self-reported health literacy and treatment adherence in older adults: a systematic review. PROSPERO 2019 CRD42019141028 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019141028

Review question

The overall objective of this study is to systematically review all published evidence on the levels and associations of self-reported health literacy and treatment adherence in older adults (over 60 years old).

It specifically aims to:

1. Examine the levels of self-reported health literacy and treatment adherence in (if available, different subgroups of) older adults

2. Evaluate the associations of self-reported health literacy and treatment adherence in older adults

3. Identify how self-reported health literacy and treatment adherence in older adults are measured

4. Investigate moderator and mediator effects of other psychosocial and sociodemographic factors (may include: Quality of life, socioeconomic status, illness perception, physical activity, age, sex)

Searches

A research librarian was consulted for advice on databases prior to the literature search.

The following five electronic databases will be searched:

PubMed, CINAHL, Cochrane Library, Epistemonikos, LIVIVO.

All databases will be searched (adapted searches) from July, 15, 2019 to July 30, 2019. Search was updated in October 2020. Searches will be limited to human subjects.

All eligible literature published until July 2019 will be included (Updated search: October 2020, included as well). Articles must be written in English or German.

In addition, articles will be searched by hand for cross-references. References will be exported to Endnote and duplicates deleted.

Search terms:

"health literacy", "illiteracy", "treatment adherence and compliance", "patient compliance", "compliance", "patient adherence", "adherence", "non-adherence", "nonadherence", "medication adherence", "discontinuation", "non-compliance", "noncompliance", "termination", "refill", "aged", "old", "older", "elderly", geriatric", "oldest", "elders".

Keywords: "health literacy", "adherence", "patient adherence", "patient compliance", "compliance", "aged", "old", "older", "elderly".

Types of study to be included

Primary research (quantitative only, baseline data) will be included. Included study types will be: Randomized controlled trials, prospective and retrospective cohort studies, and cross-sectional studies. Articles must be written in English or German.

Only original, peer-reviewed studies will be included. No systematic reviews, commentaries, conference abstracts, books, meta-analyses or grey literature will be included.

Condition or domain being studied

Levels and associations of self-reported health literacy (subjective measures) and treatment adherence in older (60+ years) adults will be assessed as primary outcomes.

Other psychosocial and sociodemographic factors will be investigated for possible moderator or mediator effects. Currently, there are no reviews that specifically focus on the associations of self-reported (subjective) outcome measures of health literacy and treatment adherence in older adults.

Participants/population

Studies that examined older adults aged 60 years and older will be included. Only studies with at least 2/3 of older adults in samples will be included.

Intervention(s), exposure(s)

Included studies must contain at least one (validated) measure of self-reported health literacy and treatment adherence and must provide at least one measure (e.g. mean) to calculate associations (i.e. correlation, effect size) between health literacy and treatment adherence.

Only studies that assessed health literacy with self-report (subjective) measures will be included. Studies that assessed health literacy with performance-based (objective) tests/ measures will not be included.

Comparator(s)/control

Different baseline levels and associations of health literacy and treatment adherence will be analyzed.

Main outcome(s)

Health literacy (subjective measure only)

Treatment adherence (including medication adherence). Treatment adherence may include pill counts, self-reports, questionnaires, screeners, and refill records.

Measures of effect

Baseline.

Additional outcome(s)

None.

Measures of effect

Not applicable.

Data extraction (selection and coding)

All search results will be exported to Endnote X8 reference management software and screened for duplicates.

Titles and abstract will be screened by two reviewers independently using a standardized checklist that will be developed for this purpose. Both reviewers will then assess full-text articles for eligibility based on clearly stated criteria. Cases of missing consensus will be discussed and, if necessary, resolved by a third reviewer. Inclusion and exclusion of all studies will be documented and presented according to PRISMA guidelines.

A data extraction sheet for data extraction from eligible studies will be developed and pilot tested, and data will be documented in Microsoft Excel.

Data extraction will include the following criteria: Title, authors, year published, journal title, assessment of health literacy and treatment adherence, psychosocial and sociodemographic outcomes with moderator and mediator effects, statistical measures to calculate associations between health literacy and treatment adherence, population and setting details, sample size, age groups, statistical significance if available.

Risk of bias (quality) assessment

Quality assessment of included full-text studies will be conducted by both reviewers using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

The NIH was deemed appropriate, since only baseline data (levels and associations of health literacy and treatment adherence) will be analyzed.

Strategy for data synthesis

Data synthesis will be conducted in accordance to PRISMA guidelines (Liberati et al., 2009).

Since only studies with subjective measures of health literacy will be included, high heterogeneity (e.g. different measures of health literacy and treatment adherence) is expected. Accordingly, a narrative synthesis will be conducted to summarize the studies thematically.

Analysis of subgroups or subsets

If available, subgroup analyses of the levels and associations of health literacy and treatment adherence in different age groups (e.g. 60-64, 65-69, 70-74, 75-79, over 80) will be conducted.

Contact details for further information

Moritz Schoenfeld
mo.schoenfeld@uke.de

Organisational affiliation of the review

University Medical Center Hamburg-Eppendorf, Department of Medical Psychology

https://www.uke.de/kliniken-institute/institute/institut-und-poliklinik-f%C3%BCr-medizinische-psychologie/index.html

Review team members and their organisational affiliations

Mr Moritz Schoenfeld. University Medical Center Hamburg-Eppendorf, Department of Medical Psychology
Mrs Stefanie Pfisterer-Heise. University Medical Center Hamburg-Eppendorf, Department of Biochemistry and Molecular Cell Biology
Professor Corinna Bergelt. University Medical Center Hamburg-Eppendorf, Deparment of Medical Psychology

Type and method of review

Narrative synthesis, Systematic review

Anticipated or actual start date

01 May 2019

Anticipated completion date

30 September 2020

Funding sources/sponsors

None.

Conflicts of interest

Language

English

Country

Germany

Stage of review

Review Completed not published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Health Literacy; Humans; Medication Adherence; Self Report

Date of registration in PROSPERO

24 October 2019

Date of first submission

12 July 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Search was updated in October 2020 and slightly adapted to possibly include newer and relevant literature. Age inclusion criteria were slightly adapted to include studies with (at least 2/3 of) participants 60 years and older, since we noticed some dissimilarities in definitions of "old age" in the studies found in our preliminary search, and decided to also include those studies as they appeared relevant to our research question.The review is now being prepared for dissemination and publication.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

24 October 2019
13 October 2020
10 March 2021

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author:
The definition of each measurement must be clarified in the study method, and if the measurement method is different, the study needs to be corrected with major drawbacks. Also, please new findings of the results from this study should be described clearly in the abstracts and conclusions.
Our answer: Thank you very much for taking the time to review our manuscript and for your comments. Indeed, we agree that the definition of measurements might not be clear enough and have corrected this accordingly. We now define medication adherence as such and excluded treatment adherence from our review since we originally aimed to review the associations between medication adherence and health literacy as represented by our search strategy and methods.
Also, we added information of our results to the abstract and conclusion sections.

Reviewer: 2

Comments to the Author:
Thank you for opportunity to review this paper. This systematic review aimed to explore the association between self-reported health literacy and treatment adherence in older adults. This study seemed to be well followed the guideline by PRISMA.
Our answer: Thank you very much for your comments and for taking the time to review our manuscript. We appreciate it very much!

The authors emphasized that this review is the first study on the association between health literacy and treatment adherence in older adults. However, it is difficult to agree to the authors' statement.
Our answer: Thank you for this important comment. Another reviewer pointed out a similar aspect. We completely agree with you. We did indeed aim to review the associations between health literacy and medication adherence, not treatment adherence, as represented in our search strategy and methods. You are correct that we did not include studies focusing on treatment adherence but only those that focused on medication adherence. Using the definition and wording of treatment adherence, we wished to address a broader audience. As treatment adherence includes medication adherence, we used both definitions somewhat interchangeably, but now realize that this leads to confusion and duplication. Accordingly, we deleted references to treatment adherence in all cases we actually meant medication adherence and changed the definition to medication adherence. Thank you again for your comment. (lines 64-65)

In introduction section, the authors presented the definition of treatment adherence by WHO. Namely, the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" From this perspective, the authors should search similar term with treatment adherence including, self-care behaviors, physical activities and diet adherence and so on.
Our answer: Thank you for your comment. We sharpened the focus of the review accordingly and emphasized that the focus of the review is on medication adherence (but not the whole broader WHO definition) (lines 64-65). A review on the associations between treatment adherence and health literacy as per the old definition and the search terms mentioned by you would indeed be interesting.

Furthermore, excepting only one study, seven studies included in this review focused on medication adherence based on their purpose. But, the authors addressed that these studies did not define the treatment adherence. I think the authors had to review the association between health literacy and medication adherence in older adults. If authors wanted to review the association between health literacy and treatment adherence, they should have searched overall similar terms with treatment adherence according to their operational definition. In this regard, please refer to below references.

Lim, M. L., van Schooten, K. S., Radford, K. A., & Delbaere, K. (2020). Association between health literacy and physical activity in older people: a systematic review and meta-analysis. Health promotion international, daaa072. Advance online publication. https://doi.org/10.1093/heapro/daaa072
Cabellos-García, A. C., Martínez-Sabater, A., Castro-Sánchez, E., Kangasniemi, M., Juárez-Vela, R., & Gea-Caballero, V. (2018). Relation between health literacy, self-care and adherence to treatment with oral anticoagulants in adults: a narrative systematic review. BMC public health, 18(1), 1157. https://doi.org/10.1186/s12889-018-6070-9

Our answer: Thank you for this important comment and your literature recommendations. While we agree with you, we did not include new search terms for treatment adherence since our aim was to examine medication adherence and health literacy, which we are optimistic we did. As explained above, we changed our definition to medication adherence. (lines 64-65)
Thank you for your literature recommendations. Both show the need for further research on health literacy and adherence in older adults as well as inclusion of different aspects of treatment adherence, which would indeed be an interesting and important addition. Since we aimed to review the associations between health literacy and medication adherence, we decided not to include further aspects of treatment adherence in our review but will consider further research into these aspects.

For method section, please explain why this review used only five databases. In case of medication adherence as main component of treatment adherence, meaningful studies may be found in EMBASE. It is not familiar with DB such as Epistemonikos, and LIVIVO

Our answer: Thank you for your comment. Unfortunately, we could not access EMBASE. However, although we did not include EMBASE as a database in our search, we are very confident that we did not miss a substantial amount of literature. Including COCHRANE as a database ensures that we did also include studies indexed in EMBASE since COCHRANE comprises at least a part of literature from EMBASE. On top of that, we used referencal hand search (e.g. from other reviews) to find additional literature. Since we are not able to include EMBASE as a database, we added this as a limitation to our dissussion. (lines 434-436)

Regarding eligibility criteria, the authors presented treatment adherence by pill counts, questionnaires, screeners, refill records. They only stand for measurement of medication adherence not overall type of treatment adherence including behavior change, diet compliance and physical activities.

Our answer: Thank you very much; this would indeed be an interesting addition. Since we changed our definition to medication adherence, we are confident that our eligibility criteria are adequate to represent the (now sharpened) aim of this review.

In table 1 and 2, the cells on the association between HL and TA are redundant.

Our answer: Yes, you are correct. Thank you for this important comment. Of course, we deleted the redundant cells in table 1. (line 235)

Especially, it should be presented the confounding factors between HL and TA to provide new knowledge on mechanism or pathway between HL and TA in older adults compared with previous systematic review in Table 3. In addition, please provide the cut off point or definition on HL such as inadequate and adequate H for studies in this review.

Our answer: Thank you for your comment and the helpful and important advice. We added confounding factors to the manuscript (table 2) as well as cut off points and categorization for health literacy and medication adherence (supplementary table S3). Interestingly, we found further discrepancies between the included studies in utilization of cutoffs and/or categorizing different levels of health literacy and/or medication adherence. We think this enhances the quality and results of the paper. (line 295)

In discussion section, the authors addressed that TA in older adults is commonly assessed by proxy of MA, which is measured with a wide range of tools. Vice versa, the authors should accurately define the range of TA for achieving the goal of reviewing literatures.

Our answer: Thank you. We agree this would be an important addition. However, since we aimed to review medication adherence and health literacy in older adults, we did not directly add these aspects to our manuscript. Nevertheless, we added further information resulting from other factors (e.g. physical activity) associated with health literacy and/or medication adherence to the discussion, again indicating the importance of future research in this field (e.g. into physical activity and health literacy as mentioned by you). (lines 355-372)

For supplementary table on search strategies, the authors should present all search query based on each five databases.
Our answer: Thank you for your recommendation. We included all search strategies in the supplement.

I hope these comments are helpful for improving quality of the paper.
Our answer: Yes, we appreciate your time and expertise in reviewing our manuscript very much and hope we were able to address all comments adequately to further improve the quality of our manuscript.

Table S1. Search strategy used in different database.	
Source of search	Search terms
PubMed (MEDLINE)	(health literacy OR illiteracy) AND (treatment adherence and compliance OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR nonadherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR termination OR refill) AND (aged OR old OR older OR elderly OR geriatric OR oldest OR elders)
CINAHL	(health literacy OR illiteracy) AND (treatment adherence and compliance OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR nonadherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR termination OR refill) AND (aged OR old OR older OR elderly OR geriatric OR oldest OR elders)
COCHRANE	health literacy OR illiteracy in Title Abstract Keyword AND treatment adherence OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR nonadherence OR termination OR refill in Title Abstract Keyword AND aged OR old OR older OR elderly OR geriatric OR oldest OR elders in Title Abstract Keyword - (Word variations have been searched)
LIVIVO	("health literacy") AND ("patient compliance and compliance" OR "patient adherence" OR adherence) AND (aged OR old OR older OR elderly)
Epistemonikos	(advanced_title_en:(health literacy OR illiteracy) OR advanced_abstract_en:(health literacy OR illiteracy)) AND (advanced_title_en:(treatment adherence OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR nonadherence OR termination OR refill) OR advanced_abstract_en:(patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR nonadherence OR termination OR refill)) AND (advanced_title_en:(aged OR old OR older OR elderly OR geriatric OR oldest OR elders) OR advanced_abstract_en:(aged OR old OR older OR elderly OR geriatric OR oldest OR elders)) [Filters: protocol=no]

PubMed Search

Search: **(health literacy OR illiteracy) AND (treatment adherence and compliance OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR nonadherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR termination OR refill) AND (aged OR old OR older OR elderly OR geriatric OR oldest OR elders)**

("health literacy"[MeSH Terms] OR ("health"[All Fields] AND "literacy"[All Fields]) OR "health literacy"[All Fields] OR ("literacy"[MeSH Terms] OR "literacy"[All Fields] OR "illiteracy"[All Fields])) AND ("treatment adherence and compliance"[MeSH Terms] OR ("treatment"[All Fields] AND "adherence"[All Fields] AND "compliance"[All Fields]) OR "treatment adherence and compliance"[All Fields] OR ("patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields]) OR ("compliances"[All Fields] OR "patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "compliance"[All Fields] OR "compliance"[MeSH Terms]) OR ("patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR ("patient"[All Fields] AND "adherence"[All Fields]) OR

"patient adherence"[All Fields]) OR ("adherance"[All Fields] OR "adhere"[All Fields] OR "adhered"[All Fields] OR "adherence"[All Fields] OR "adherences"[All Fields] OR "adherent"[All Fields] OR "adherents"[All Fields] OR "adherer"[All Fields] OR "adherers"[All Fields] OR "adheres"[All Fields] OR "adhering"[All Fields]) OR "non-adherence"[All Fields] OR ("nonadherence"[All Fields] OR "nonadherent"[All Fields] OR "nonadherents"[All Fields] OR "nonadherers"[All Fields]) OR ("medication adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "medication adherence"[All Fields]) OR ("discontinuance"[All Fields] OR "discontinuances"[All Fields] OR "discontinuated"[All Fields] OR "discontinuation"[All Fields] OR "discontinuations"[All Fields] OR "discontinue"[All Fields] OR "discontinued"[All Fields] OR "discontinuer"[All Fields] OR "discontinuers"[All Fields] OR "discontinues"[All Fields] OR "discontinuing"[All Fields]) OR "non-compliance"[All Fields] OR ("noncompliant"[All Fields] OR "noncompliants"[All Fields] OR "noncompliers"[All Fields] OR "noncomplying"[All Fields] OR "patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "noncompliance"[All Fields] OR "noncompliances"[All Fields]) OR ("terminal"[All Fields] OR "terminal s"[All Fields] OR "terminally"[All Fields] OR "terminals"[All Fields] OR "terminate"[All Fields] OR "terminated"[All Fields] OR "terminates"[All Fields] OR "terminating"[All Fields] OR "termination"[All Fields] OR "terminations"[All Fields] OR "terminator"[All Fields] OR "terminators"[All Fields]) OR ("refill"[All Fields] OR "refillable"[All Fields] OR "refilled"[All Fields] OR "refilling"[All Fields] OR "refills"[All Fields])) AND ("aged"[MeSH Terms] OR "aged"[All Fields] OR "old"[All Fields] OR ("older"[All Fields] OR "olders"[All Fields]) OR ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("geriatric"[All Fields] OR "geriatrics"[MeSH Terms] OR "geriatrics"[All Fields]) OR "oldest"[All Fields] OR ("elder s"[All Fields] OR "elders"[All Fields] OR "sambucus"[MeSH Terms] OR "sambucus"[All Fields] OR "elder"[All Fields]))

Table S1. Risk of Bias of reviewed studies based on NHLBI.

Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total[1]
Lee et al., 2013	+	+	NR	+	-	-	-	+	+	-	+	-	NA	+	fair
Lee et al., 2017	+	+	+	+	+	-	-	-	+	-	+	-	NA	+	fair
Lu et al., 2019	+	+	+	+	+	-	-	-	+	-	+	NR	NA	+	fair
Reading et al., 2019	+	+	+	+	-	-	-	+	-	-	-	NR	NA	+	poor
Saqlain et al., 2019	+	+	+	+	+	-	-	+	+	-	+	-	NA	+	fair
Seong et al., 2019	+	+	NR	+	+	-	-	+	+	-	+	NR	NA	+	fair
Shehadeh-Sheeny et al., 2013	+	+	+	+	-	-	-	+	+	-	+	-	NA	+	fair
Song & Park, 2020	+	+	+	+	+	-	-	-	+	-	+	NR	NA	+	fair
Wannasirikul et al., 2016	+	+	+	+	+	-	-	+	+	-	+	-	NA	+	fair

Notes and abbreviations: [1]Total scores were calculated based on the single scores and a critical appraisal of the methodological quality of each study in accordance with the NHLBI. NR: Not relevant, NA/NR: Not available/not reported.

Criteria: 1. Was the research question or objective in this paper clearly stated?; 2. Was the study population clearly specified and defined?; 3. Was the participation rate of eligible persons at least 50%?; 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?; 5. Was a sample size justification, power description, or variance and effect estimates provided?; 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?; 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?; 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?; 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; 10. Was the exposure(s) assessed more than once over time?; 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; 12. Were the outcome assessors blinded to the exposure status of participants?; 13. Was loss to follow-up after baseline 20% or less?; 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?.

The NHLBI can be found in: National Heart, Lung, and Blood Institute. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. 2014. Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort.

Table S3. Cutoffs and categorization of measures of health literacy and medication adherence

Authors, year	HL measures	Reported range and cutoff/ categories of HL scores	MA measure	Reported range and cutoff/ categories of MA scores
Lee *et al.*, 2013	BHLS 3 questions	Range of overall HL scores: 3-15 with higher scores indicating higher HL Cutoff/ categories: NA	MMAS-4	Range of overall MA scores: 0-4 with higher scores indicating higher MA Cutoff/ categories: MA scores were dichotomized into nonadherence (scores ≤ 2) and adherence (scores ≥3)
Lee *et al.*, 2017	BHLS 15 questions	Range of overall HL scores: 15-75 with higher scores indicating higher HL Cutoff/ categories: NA	MMAS-8	Range of overall MA scores: 0-8 with higher scores indicating higher MA Cutoff/ categories: Scores were categorized into high (scores of 8), medium (scores 6-7), and low (scores ≤5) MA
Lu *et al.*, 2019	HLS-EU-Q16	Range of overall HL scores: 0-50 with higher scores indicating higher HL Cutoff/ categories: Scores ≤33 indicated limited HL, scores >34 indicated adequate HL	MOS-SAS	Range of MA scores: 0-5 with higher scores indicating higher MA Cutoff/ categories: Scores were dichotomized into adherence (scores ≥4) and nonadherence (scores ≥3)
Reading *et al.*, 2019	BHLS 3 questions	Range of overall HL scores: 3-15 with higher scores indicating higher HL Cutoff/ categories: HL was dichotomized into adequate and inadequate, but no cutoffs were reported	CARDIA (3 questions)	Range of MA scores: NA Cutoff/ categories: Nonadherence was defined according to scale for each answer (1. answers "75% of the time" or less; 2. /3. answers "once per week" or more)
Saqlain *et al.*, 2019	SILS	Range of overall HL scores: 1-5 with higher scores indicating lower HL Cutoff/ categories: HL scores ≥3 indicated inadequate HL and scores ≤2 indicated adequate HL	MMAS-4	Range of overall MA scores: 0-4 with higher scores indicating higher MA Cutoff/ categories: MA scores were dichotomized into nonadherence (scores ≤ 3) and adherence (scores of 4)
Seong *et al.*, 2019	BHLS 3 questions	Range of overall HL scores: 0-12 with higher scores indicating higher HL Cutoff/ categories: HL scores were categorized into inadequate (scores ≤6), marginal (scores 7-10), and adequate (scores 11-12) HL	Single item ("In the past week, have you forgotten to take your antithrombotic medication for various reasons?")	Range of overall MA scores: 1-5 with higher scores indicating higher MA Cutoff/ categories: MA scores were dichotomized into nonadherence (scores ≤ 5) and adherence (scores of 6)
Shehadeh-Sheeny *et al.*, 2013	FCCHL	Range of overall HL scores: NA, higher scores indicating higher HL Cutoff/ categories: HL scores were categorized into low, medium, and high HL, but no cut offs were reported/ are available	MPR	Range of overall MA scores: 0-1 (0%-100%), higher scores indicating higher MA Cutoff/ categories: MA scores were categorized into low (MPR ≤ 0.2) and high (MPR ≥ 0.8) MA

Song & Park, 2020	BHLS 15 questions	Range of overall HL scores: 15-75 with higher scores indicating higher HL Cutoff/ categories: NA	MMAS-8	Range of overall MA scores: 0-8 with higher scores indicating higher MA Cutoff/ categories: NA
Wannasirikul *et al*., 2016	FCCHL	Range of overall HL scores: 17-68 with higher scores indicating higher HL Cutoff/ categories: HL scores were categorized into inadequate, marginal, and adequate HL, but no cut offs were reported/ are available	ARMS	Range of overall MA scores: 14-56 with higher scores indicating higher MA Cutoff/ categories: NA

Abbreviations: BHLS: Brief Health Literacy Screen, MMAS: Morisky Medication Adherence Scale, HLS-EU-Q: European HL Survey Questionnaire, MOS-SAS: Medical Outcomes Study Specific Adherence Scale, CARDIA: Coronary Artery Risk Development in Young Adults, SILS: Single Item Literacy Screener, FCCHL: Functional, Communicative, and Critical Health Literacy Questionnaire, MPR: Medication Possession Ratio, ARMS: Adherence to Refills and Medications Scale, NA: Not available/ not reported.

BMJ Open

Self-reported health literacy and medication adherence in older adults: A systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-056307.R1
Article Type:	Original research
Date Submitted by the Author:	03-Oct-2021
Complete List of Authors:	Schönfeld, Moritz; University Medical Center Hamburg-Eppendorf, Department of Medical Psychology Pfisterer-Heise, Stefanie; University Medical Center Hamburg-Eppendorf, Department of Biochemistry and Molecular Cell Biology Bergelt, Corinna; University Medical Center Hamburg-Eppendorf, Department of Medical Psychology; University Medicine Greifswald, Institute of Medical Psychology
Primary Subject Heading:	Public health
Secondary Subject Heading:	Geriatric medicine, Research methods
Keywords:	PUBLIC HEALTH, GERIATRIC MEDICINE, STATISTICS & RESEARCH METHODS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Self-reported health literacy and medication adherence in older adults: A systematic review

Schönfeld MS[1], Pfisterer-Heise S[2], Bergelt C[1,3]

[1] Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
[2] Department of Biochemistry and Molecular Cell Biology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
[3] Department of Medical Psychology, University Medicine Greifswald, Greifswald, Germany

Corresponding author:
Moritz Sebastian Schönfeld
University Medical Centre Hamburg-Eppendorf
Department of Medical Psychology
Martinistrasse 52
20246 Hamburg
Germany
mo.schoenfeld@uke.de
Tel: +49-40-7410-59140

Word count
5,463 words

Date and version
First submission of manuscript: October 29, 2020
1. Resubmission of revised manuscript: August 10, 2021
2. Resubmission of revised manuscript: August 26, 2021
3. Resubmission of revised manuscript: October 1, 2021

Abstract

Objectives. To give an overview over the associations between self-reported health literacy and medication adherence in older adults.

Design A systematic literature review of quantitative studies published in English and German.

Data sources. MEDLINE via PubMed, CINAHL, Cochrane Library, Epistemonikos, and LIVIVO were searched.

Eligibility criteria. Included studies had to examine the associations between self-reported health literacy and medication adherence in the elderly (samples including ≥66% of ≥60 years old), had to use a quantitative methodology and had to be written in English or German.

Data extraction and synthesis. All studies were screened for inclusion criteria by two independent reviewers. A narrative synthesis was applied to analyse all included studies thematically. Quality assessment was conducted using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI).

Results. We found 2,313 studies of which nine publications from eight studies were included in this review. Five studies reported a majority of participants with limited health literacy, one study reported a majority of participants with adequate health literacy, and three publications from two studies only reported mean levels of health literacy. Eight publications from seven studies used self-reports to measure medication adherence, while one study used the medication possession ratio. Overall, six publications from five studies reported significantly positive associations between health literacy and medication adherence while two studies reported positive but nonsignificant associations between both constructs and one study reported mixed results.

Conclusion. In this review, associations between self-reported health literacy and medication adherence are rather consistent indicating positive associations between both constructs in older adults. However, concepts and measures of health literacy and medication adherence applied in the included studies still show a noteworthy amount of heterogeneity (e.g. different use of cutoffs). These results reveal the need for more differentiated research in this area.

PROSPERO registration number. CRD42019141028.

Strengths and limitations of this study

- To our knowledge, this is the first systematic review to specifically give an overview of existing literature on the association between self-reported health literacy and medication adherence in older adults.
- The review protocol was registered prospectively, and the review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
- Overall, the included studies showed a considerable level of heterogeneity, and the quality of the included studies was predominantly fair, which is a limitation of this review.
- Health literacy is still commonly assessed with performance-based measures, making literature searches for self-reports in this field challenging.

INTRODUCTION

Within the last decades, demographic change and increasing life expectancy have put older adults (≥60 years old as defined by the United Nations[1]) in the focus of health care research. With increasing age, the risk of chronic diseases and comorbidities rises resulting in a growing number of necessary treatments (e.g. medication), and adherence to these treatments becomes crucial to reduce adverse reactions and ensure safe and effective care. In this context, health literacy (HL), often defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions"[2], has been identified as a key influencing factor of improving health-related behaviour in the elderly[3]. Accordingly, (elderly) people with low levels of HL use health care more often and show higher rates of hospitalization than those with high levels of HL[3 4].

Research also confirmed low HL as a predictor of poor health outcomes linking lower HL to higher age[5 6], lower income[5] and lower education[3 7]. In addition, HL has been repeatedly linked to medication adherence, commonly defined as "the extent to which a patient's behaviour corresponds with the prescribed medication dosing regime, including time, dosing and interval of medication intake"[8]. Medication adherence (MA) has been the focus of this research since the number of medications taken commonly increases with increasing age, making medication the most common form of therapy in the elderly, often resulting in polypharmacy[9 10]. Thus, MA still plays a crucial role in the elderly patient´s care. However, research into the associations between HL and MA stays inconclusive[11-16]. While multiple studies report (significantly) positive associations between HL and MA[17-21], others report (significantly) negative associations[22 23].

Systematic reviews specifically conducted to analyse the relationship between HL and MA in the elderly resulted in mixed findings as they often included studies with a variety of populations and measures of HL[12 16 24]. Older adults have commonly been examined as a homogenous group not taking into account possible differences in levels of HL and MA between subgroups of age (e.g. 65-70 years old, 71-75 years old, 76-80 years old, 85+ years old[6 25]). In addition, reviews and meta-analyses examining the associations between HL and MA in older age commonly included samples with a wide age range only focusing on the mean age of samples. Since these samples often include (undisclosed) proportions of younger adults and subgroups are not reported, results may not adequately reflect the relationship between HL and MA in older adults[24 26]. Previous reviews commonly aimed to include a wide selection of validated measures of HL. However, since only a low proportion of relevant studies are measuring HL with self-reports, these reviews often resulted in a focus on the so-called legacy instruments of HL (i.e. REALM[27], TOFHLA[28])[12 24] and thus included different measures and concepts of HL, which may have led to unknown bias[15 26]. As recently stated by Nguyen *et al*.[29], these often-deployed legacy tools may measure different aspects of literacy and may not be appropriate to assess HL in older adults. Accordingly, limited HL was found to be strongly associated with older age when measured with the TOFHLA (mainly assessing reading, comprehension and numeracy skills[28]) while limited HL had weak associations with older age[30] when measured with the REALM (mainly assessing medical vocabulary[27]).

As of late, these methodological shortcomings in research into HL have been increasingly recognized leading to a broader discussion about the conceptualization and measurement of HL. Most recently, researchers started concentrating on self-report measures of HL as new questionnaires from more comprehensive concepts were developed (e.g. the HLS-EU-Q[31]). Compared to performance-based measures, self-reports of HL commonly offer a fast, easy, and inexpensive way to collect data and have a lower risk of stigma[29]. Accordingly, self-reports present important advantages when assessing HL in

different populations and contexts as they can be applied more effortless. More recently, some studies began to investigate levels of HL in different subgroups of older age resulting in a renewed call for more differentiated methods and analyses in this population[25 32].

Thus, our review aims to systematically review the evidence on self-reported HL and MA in older adults (≥60 years old) including: 1. the levels of self-reported HL and MA (if available, levels of different subgroups); 2. the associations between self-reported HL and MA; 3. how self-reported HL and MA are measured; and (if available) 4. moderator and mediator effects of other psychosocial factors.

METHODS

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[33]. A checklist of PRISMA items can be found in online supplementary file S1. This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42019141028. The protocol is presented in online supplementary file S2.

Eligibility criteria

Population. Studies examining elderly adults aged 60 years and older were included. In case of study samples with a wider age range, only studies with ≥66% of participants 60 years and older were included to ensure only including studies with a majority of older adults.

Intervention. No specific interventions were included in the criteria. Nevertheless, only studies that assessed associations (e.g. correlation, effect size) between self-reported HL and MA were deemed eligible. Studies that assessed HL solely with a performance-based test instrument (e.g. REALM[27], TOFHLA[28]) were excluded from this review.

Outcomes. Studies examining HL with a validated self-report (subjective measure) as well as MA (measured by e.g. questionnaires, refill records) were included.

Study design. Only primary quantitative research (RCTs, prospective and retrospective cohort studies, and cross-sectional studies) published in English or German was included. In case of multiple time-points, only baseline data was included to ensure comparability.

Data sources and search strategy

An electronic search was performed in five electronic databases (MEDLINE via PubMed (1984-2021), CINAHL (1995-2021), Cochrane Library (1997-2021), Epistemonikos (1995-2021), LIVIVO (1966-2021)) between July 15 and July 30, 2019 by the first author and updated again in July 2021. The search was not limited to a specific time frame. A comprehensive search strategy was applied using combinations of the following search terms: “Health literacy", “illiteracy”, “treatment adherence and compliance”, “patient compliance”, “compliance”, “patient adherence” “adherence”, “non-adherence”, “nonadherence”, “medication adherence”, “discontinuation”, “non-compliance”, “noncompliance”, “termination”, “refill”, "aged”, “old”, “older”, “elderly”, “geriatric”, “oldest”, “elders”. As these databases use partially different search algorithms, the search strategy was adapted using MeSH-Terms and Boolean operators (“AND”, “OR”) if applicable (online supplementary table S1). Although this systematic review focuses on self-reports of HL, the terms “self-report” or “subjective” were not included for reasons of higher sensitivity.

In addition, reference lists from eligible articles were hand searched accordingly. All references were subsequently imported into Endnote X8 reference management software for screening purposes.

Study selection and screening

After removal of duplicates, two raters (MSS, SPH) screened titles and abstracts of all remaining studies for eligibility. A checklist was developed for this purpose which included a list of inclusion and exclusion criteria, such as type of measure of HL, MA, and included sample, to allow for a careful screening process. As many studies include HL only as a secondary outcome and may thus not state it in the study's title or abstract, a more liberal title/ abstract screening was conducted. Accordingly, two raters (MSS, SPH) assessed the full texts of all previously screened studies independently. Figure 1 shows specific reasons for study exclusion, which included lack of self-report HL measure, lack of MA measure, lack of associations between HL and MA, lack of older adults in sample, lack of English or German language, being an ongoing clinical trial with no results, lack of primary research (e.g. book chapter), lack of quantitative data (e.g. interview study), or several of these reasons. In case of discrepancies, conflicts were discussed until consensus was reached.

Quality assessment

The methodological quality of all studies included in this review was assessed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, NIH[34]). Since only baseline data from quantitative research was included, the NHLBI was deemed appropriate. The NHLBI contains 14 criteria mainly to assess the internal validity of a study. Each item was answered "yes" (if criterion was met), "no" (if criterion was not met) or "cannot determine/ not applicable/ not reported". As the NHLBI is not meant to assess the study quality by simply summing up its scores, an overall quality rating ("good", "fair", "poor") for each study included a comprehensive and critical appraisal of each criterion as well as the study as a whole.

Data extraction and synthesis

All relevant data was extracted by the first author with the help of a data extraction checklist that was developed for this purpose and contained the following information about each included study: title, authors, year published, study design and setting, sample and sample size, age subgroups, definition and assessment of HL and MA, moderator and mediator effects (if available), statistical measures to calculate associations between HL and MA (e.g. correlation), statistical significance if available.

As the studies showed heterogeneity due to differences in study design, participants, risk of bias, and operationalization of HL and MA (e.g. different use of cutoffs and levels of HL), a narrative synthesis was applied to analyse the studies thematically.

Patient and public involvement

Patients or the public were not involved in this study.

RESULTS

Search results

The literature search resulted in a total of 2,313 studies after removal of duplicates. After screening for title and abstract another 1,769 studies were excluded based on exclusion criteria (figure 1). Full texts of 544 studies were screened and nine publications from eight studies met all eligibility criteria and were thus included in this review (figure 1). The main reason for study exclusion in the screening process was lack of self-reports of HL measure.

Study characteristics

Overall study characteristics are presented in table 1. All included publications were published between 2013 and 2020 with sample sizes between n=116 and n=12,159 (Median=293). The proportion of female participants ranged from 33% to 100% (Median=53.6%). All studies adopted a cross-sectional design (5 survey studies). Three studies (four publications) were conducted in South Korea, and one study each in China, USA, Pakistan, Israel, and Thailand. Studies were conducted across settings of tertiary care hospitals (n=5), primary health care (n=1), private health care centres (n=1), community health care centres (n=1), and clinics (n=1). All studies examined patients/adults with different types of (chronic) diseases: hypertension (n=2), heart diseases (n=1), atrial fibrillation (n=2), osteoporosis (n=1), several chronic diseases (n=3). Due to eligibility criteria restricting included samples to those with ≥66% of older adults (60 years of age and older), all studies focused on the elderly and only two studies also included patients younger than 60 years (table 1). Five studies included samples with a higher proportion of women.

Risk of bias

Study quality in terms of risk of bias was considered poor for one publication and fair for eight publications (online supplementary table S2). In most cases, risk of bias occurred from lack of randomization, blinding, and longitudinal data.

Health literacy – key findings

In five publications from four studies[35-39] self-reported HL was measured using a selection of questions from the Brief Health Literacy Screen (BHLS[40]). The BHLS employs three to fifteen questions (e.g. "How often do you have someone help you read hospital materials?") to identify people with inadequate levels of HL. Another study[41] used the short version of the European Health Literacy Survey Questionnaire (HLS-EU-Q) which was designed by the HLS-EU-Consortium based on a conceptual framework of HL[31]. One study assessed HL with the Single Item Literacy Screener (SILS), which asks ""How often do you need to have someone help when you read instructions, pamphlets, or other written material from your doctor or pharmacy?"[42]. Another two studies adopted the Functional, Communicative, and Critical Health Literacy questionnaire (FCCHL) developed by Ishikawa *et al*.[43], a validated questionnaire that assesses three areas of HL: functional HL, communicative HL, and critical HL.

Results on the overall levels of HL were mixed, yet a tendency towards limited HL (i.e. marginal, low, inadequate) in the elderly was observable. While three publications from two studies[35 36 39] only reported mean levels of HL in samples patients aged 65 years and older, six studies reported different levels of HL (e.g. marginal, low, or adequate HL). Three of these six studies[38 41 44] used cut-offs recommended by the original authors of the assessment instruments whereas three studies[37 45 46] did not report how they calculated HL scores. Five of these six studies[38 41 44-46] found that a majority of the respective samples reported limited HL levels (i.e. more people had low scores of HL; range from 62.6% to 92.5%,

Median=74.5%) whereas one study[37] found that a majority of the sample reported adequate levels of HL (i.e. more people had high scores of HL; 76.9%).

Medication adherence – key findings

Four publications from three studies[35 36 39 44] employed versions of the Morisky Medication Adherence Scale (MMAS[47]) to assess MA. The MMAS consists of four to eight questions asking about different aspects of medication intake behaviour (e.g. "Do you sometimes forget to take your medication?"[47]). One study[41] used the Medical Outcomes Study Specific Adherence Scale (MOS-SAS[48]) which addresses MA ("How often have you done each of the following in the past 4 weeks: Took medication as prescribed (on time without skipping dosis)?") as well as heart-healthy lifestyle behaviour (i.e. six preventive behaviours for coronary heart disease, e.g. low-salt diet). One study[38] used a single-item adopted from Wu *et al*.[49] to assess MA ("In the past week, have you forgotten to take your antithrombotic medication for various reasons?"). Another study[37] adopted three questions from the Coronary Artery Risk Development in Young Adults (CARDIA[50]) to assess MA (1. "In the past month, how often did you take your medications as the doctor prescribed?"; 2. "In the past month, how often did you forget to take 1 or more of your prescribed medications?"; 3. "In the past month, how often did you decide to skip 1 or more of your prescribed medications?"). MA was also assessed by the Medication Possession Ratio (MPR) in one study[45]. The MPR commonly represents the period during which a patient has an adequate amount of supply of his/her medication available over a predefined amount of time (e.g. a year). One study assessed MA with the Adherence to Refills and Medication Scale (ARMS[51]) which assesses if a patient can correctly take and refill his or her medication on schedule.

Overall, five publications from four studies[35 36 38 44 45] found that a majority of the sample reported low levels of MA (i.e. more non-adherers; range from 50.2% to 69.4%, Median=59.0%) while three studies[37 41 46] in contrast, found that a majority of the sample reported high levels of MA (i.e. more adherers; range from 84.7% to 98.3%, Median=93.7%). One study reported a sample mean score of MA only[39].

Table 1. Overall summary of included studies

Authors, year	Setting, country	Sample					Risk of bias[1]
		N	Age (years), mean (±SD)	% Female	Age subgroups	Disease	
Lee *et al.*, 2013[35]	Tertiary care hospitals, South Korea	n=293	65+ M=74.4 (6.3)	46.8%	NA	Chronic Diseases	fair
Lee *et al.*, 2017[36]	Tertiary care hospital, South Korea	n=291	65+ M=NA	53.6%	65-74 (57.0%) ≥75 (43.0%)	Chronic Diseases	fair
Lu *et al.*, 2019[41]	Tertiary care hospital, China	n=598	M=65.8 (9.4)	33.3%	≤60 (21.5%) 61-70 (43.0%) 71-80 (29.7%) ≥81 (5.7%)	Coronary Heart Disease	fair
Reading *et al.*, 2019[37]	Private care centres, USA	n=12159	21+ 72.7 (64.4-79.9†, adherent patients) 70.1 (59.5-79.1†, nonadherent patients)	43.0%	<65 (27.2%) 65-74 (30.8%) 75-84 (30.5%) ≥85 (11.5%)	Atrial Fibrillation	poor
Saqlain *et al.*, 2019[44]	Tertiary care centres, Pakistan	n=262	65+ M=NA	64.5%	65-75 (84.7%) 76-85 (11.1%) >85 (4.2%)	Hypertension	fair
Seong *et al.*, 2019[38]	Tertiary general hospital, South Korea	n=277	65+ M=74.2 (7.2)	40.8%	65-70 (32.1%) 70-79 (45.5%) ≥80 (22.4%)	Atrial Fibrillation	fair
Shehadeh-Sheeny *et al.*, 2013[45]	Clinics, Israel	n=303	60+ M=71 (6.04)	100%	60-65 (21.5%) 66-75 (54.1%) 76-85 (24.4%)	Osteoporosis	fair
Song & Park, 2020[39]	Community Health Centre, South Korea	n=116	65+ M=72.7 (6.1)	69.8%	65-69 (38.8%) 70-79 (43.1%) ≥80 (18.1%)	Chronic Diseases	fair
Wannasirikul *et al.*, 2016[46]	Primary Care Centre, Thailand	n=600	60-70 M=65.3 (NA)	75.8%	60-65 (52.7%) 66-70 (47.3%)	Hypertension	fair

Notes and abbreviations. † Median (Interquartile range).[1] Risk of Bias was measured using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, NIH[34]). NA: Not available/ not reported.

Age subgroups – key findings

Seven studies[36-39 41 44 45] included in this review examined age subgroups for differences in HL and/or MA. All of these studies conducted subgroup analyses for differences in MA while only one of these studies[41] examined differences in HL between age subgroups (e.g. 65-75 years old, 76-85 years old, >85 years old; table 2).

Overall, four studies[36 41 44 45] found no significant differences in MA between age subgroups while one study[37] reported age as a significant predictor of medication nonadherence as younger patients (<65 years old) were more likely to be nonadherent compared to old/older patients (age groups 65-74 years old and 75-84 years old) but not compared to the oldest (≥85 years old). One study[39] reported higher MA in 65-69-year-old adults compared to 70-79-year-old adults and ≥80-year-old adults. Another study[38] reported significant differences in adherence levels between age subgroups but did not confirm age as a significant predictor of medication nonadherence in multivariate analyses. Age was significantly associated with HL in one study[41] as patients with limited HL were significantly older compared to those with adequate HL. However, regression analyses did not confirm age as a predictor of limited HL (table 2).

Table 2. Results of age subgroup analyses on associations between age and health literacy, and age and medication adherence

Authors, year	Age subgroups reported	Age subgroup analyses
Lee *et al.*, 2013[35]	NA	None conducted
Lee *et al.*, 2017[36]	65-74 (57.0%) ≥75 (43.0%)	No significant differences in MA between age groups (χ^2=0.391, p=0.835)
Lu *et al.*, 2019[41]	≤60 (21.5%) 61-70 (43.0%) 71-80 (29.7%) >81 (5.7%)	Patients with limited HL were significantly older than those with adequate HL (p<0.05) Age was not a significant predictor for limited HL in ≥81-year-old patients compared to - patients ≤60 years old (AOR (95% CI) = 0.64 (0.24-1.72), p=0.380) - patients 61-70 years old (AOR (95% CI) = 1.19 (0.49-2.88), p=0.694) - patients 71-80 years old (AOR (95% CI) = 0.97 (0.40-2.40), p=0.955) Age was not a significant predictor for medication nonadherence in ≥81-year-old patients compared to - patients ≤60 years old (AOR (95% CI) = 0.67 (0.19-2.36), p=0.534) - patients 61-70 years old (AOR (95% CI) = 1.43 (0.49-4.17), p=0.518) - patients 71-80 years old (AOR (95% CI) = 1.02 (0.34-3.09), p=0.970)
Reading *et al.*, 2019[37]	<65 (27.2%) 65-74 (30.8%) 75-84 (30.5%) ≥85 (11.5%)	Nonadherence to medication significantly differed according to age (p<0.001) Age was a significant predictor for nonadherence to medication in <65-year-old patients compared to - patients 65-74 years old (AOR (95% CI) = 0.68 (0.55-0.83), p<0.001) - patients 75-84 years old (AOR (95% CI) = 0.67 (0.53-0.84), p<0.001) Age was not a significant predictor for nonadherence to medication in <65-year-old patients compared to - patients ≥85 years old (AOR (95% CI) = 0.86 (0.64-1.16), n.s.)
Saqlain *et*	65-75 (84.7%)	No significant differences in MA between age groups (χ^2=1.631, p=0.442)

al., 2019[44]	76-85 (11.1%) >85 (4.2%)	
Seong *et al*., 2019[38]	65-70 (32.1%) 70-79 (45.5%) ≥80 (22.4%)	Adherence to medication significantly differed with respect to age (χ^2=15.15, p<0.001) Age was a significant predictor for nonadherence to medication in ≥80-year-old patients (univariate regression) compared to - patients ≤79 years old (OR (95% CI) = 2.33 (1.291-4.207), p=0.005, univariate) Age was not a significant predictor for nonadherence to medication in ≥80-year-old patients (multivariate regression) compared to - patients ≤79 years old (OR (95% CI) = 1.24 (0.621-2.459), p=0.546, multivariate)
Shehadeh-Sheeny *et al*., 2013[45]	60-65 (21.5%) 66-75 (54.1%) 76-85 (24.4%)	No significant differences in MA between age groups (p=0.23)
Song & Park, 2020[39]	65-69 (38.8%) 70-79 (43.1%) ≥80 (18.1%)	Adherence to medication significantly differed with respect to age (Z=8.37, p<0.001). Post hoc analysis showed higher MA in 65-69-year-old adults (M=5.1 (2.3)) compared to 70-79 (M=4.0 (2.0)) and ≥80-year-old adults (M=3.0 (1.9)), respectively.
Wannasirikul *et al*., 2016[46]	60-65 (52.7%) 66-70 (47.3%)	None conducted

Notes: NA: Not available/ not reported.

Associations between health literacy and medication adherence

Results of the analyses on associations between HL and MA are depicted in table 3. In addition, an overview of cutoffs and categories used for the measures of HL and MA in the included studies are depicted in online supplementary table S3. All studies conducted analyses on these associations. Overall, six publications from five studies[35-37 39 44 46] reported positive and statistically significant associations between HL and MA while two studies[41 45] did not find any significant associations, and one study[38] reported mixed findings. In detail, one of two publications[35] from one study confirmed HL as the strongest predictor for MA in a hierarchical regression analysis while another publication[35] from this study found significantly positive associations between HL and MA but reported self-efficacy to be the strongest predictor for HL in their support vector machine (SVM) model. Another study[41] found no significant differences between limited compared to adequate HL in (medication) nonadherent patients with coronary heart disease. However, the study reported that patients with limited HL were more likely to be nonadherent to secondary adherence measures (i.e. heart-healthy lifestyle, alcohol intake control, exercise, stress management) and suggested that changing how to take your pills may be easier than changing lifestyle behaviour. In a study among ethnically diverse patients with atrial fibrillation[37], patients with inadequate levels of HL were significantly more likely to be nonadherent to medication than those with adequate levels of HL. In addition, the study found that included patients with self-reported physical inactivity (vs. physical activity), alcohol use (vs. no alcohol use), and diabetes mellitus were more likely to be nonadherent to medication, whereas patients with diagnosis of hypertension were less likely to be nonadherent to medication. A study on outpatients with hypertension[44] found positive and statistically

significant associations between HL and MA as well as a higher likelihood of patients with adequate levels of HL to be adherent to medication compared to patients with inadequate levels of HL. In their multivariate logistic regression, the same study found that in addition to adequate HL, self-reported good and moderate subjective health as well as independence in activities of daily living were also independent predictors of MA in the elderly. Another study[38] reported significant differences in adherence to antithrombotic medication by levels of HL but did not confirm HL as a significant predictor for MA in older adults. They concluded that a significant association between HL and MA might exist still since in their univariate regression the rate of inadequate HL was higher in the group of nonadherent patients compared to adherent patients. However, in their multivariate logistic regression, the authors[38] found only cognitive impairment to be a significant predictor of medication nonadherence in older patients with atrial fibrillation. One study[45] found no significant association between HL and MA in a population of female osteoporosis patients and found only self-reported income to be a significant predictor of adherence in the conducted multivariate logistic regression. Another study[39] found significantly positive associations between HL and MA. In their multiple regression analysis, the authors also found that income, number of chronic diseases, vision problems, and HL were significant predictors of MA. One other study[46] analysed the relationship between HL, MA, and blood pressure levels in primary care patients with hypertension using a Structural Equation Modeling (SEM) approach, which supported the existence of a causal relationship between these factors. Accordingly, HL had a positive but small statistically significant direct effect on MA. Literacy and cognitive ability had the biggest direct effects on both HL and MA. Additionally, HL had the biggest significantly negative direct effect on blood pressure levels (i.e. the higher the HL, the lower the blood pressure level). Based on the SEM, the authors of this study[46] suggested a mediator effect of HL on MA, even though no analysis was conducted. None of the other studies performed mediator and/or moderator analyses concerning HL and/or MA and other factors

308

Table 3. Detailed analyses of health literacy and medication adherence

Authors, year	Sample and setting	HL measures	MA measure	Key results	Associations between HL and MA and further outcomes
Lee *et al.*, 2013[35]	n=293, 65+ years M=74.4 years (6.3) Patients with chronic diseases from tertiary care hospitals in Cheonan, South Korea	BHLS 3 questions	MMAS-4	Mean HL was 8.3 (1.9) n=120 (41.0%) patients were adherent to medication	Significant associations between HL and MA (p=NA) Self-efficacy was strongest predictor for MA in SVM model Other factors significantly associated with MA were number of medication types, daily pill counts, duration after diagnosis
Lee *et al.*, 2017[36]	n=291, 65+ years M=NA Patients with chronic diseases from tertiary care hospital in South Korea	BHLS 15 questions	MMAS-8	Mean HL was 46.61 (12.66) n=89 (30.6%) patients were highly adherent with MMAS-Score of 8 Mean MA was at a medium level (M=6.32 (1.61))	HL positively correlated with MA (r=0.25, p<0.001) HL was strongest predictor of MA in hierarchical linear regression (β=0.190, p<0.001) Other significant predictors of MA in regression were perceived health status (β=0.132, p<0.02), use of magnifying glass (β=0.166, p<0.003), assistance with medication administration (β=0.120, p<0.035)
Lu *et al.*, 2019[41]	n=598 M=65.8 years (9.4) Patients with coronary heart disease from tertiary hospital in Shanghai, China	HLS-EU-Q16	MOS-SAS	HL was limited for n=444 (74.5%) and adequate for n=152 (25.5%) patients Patients with limited HL were significantly older than those with adequate HL (p=0.003) n=505 (84.7%) patients were adherent to medication	No significant associations between HL and MA (χ^2=NA, p=0.125) No significant predictive relationship between limited HL and medication nonadherence (AOR (95% CI) = 0.66 (0.39-1.11), p=0.113) Patients with limited HL compared to those with adequate HL were more likely to be nonadherent to overall heart-healthy lifestyle behaviour (AOR (95% CI) = 1.69 (1.13-2.53), p=0.010), exercise (AOR (95% CI) = 1.50 (1.01-2.22), p=0.046), alcohol intake control (AOR (95% CI) = 2.19 (1.21- 3.96), p=0.010), and stress management (AOR (95% CI) = 2.09 (1.32-3.29), p=0.002)
Reading *et al.*, 2019[37]	n=12159, 21+ years Age median was 72.7 and 70.1 years for adherent and nonadherent patients, respectively Ethnically diverse patients with atrial fibrillation from Northern California, USA	BHLS 3 questions	CARDIA (3 questions)	n=9349 (76,9%) patients had adequate HL n=771 (6.3%) patients were nonadherent to medication Significant differences in MA between age subgroups (p<0.001)	Patients with inadequate HL were more likely to be nonadherent to medication compared to those with adequate HL (AOR (95% CI) = 1.32 (1.09-1.60), p<0.01) in multivariate logistic regression model Patients were more likely to be nonadherent to medication if physically inactive (AOR (95% CI) = 1.57 (1.16-2.13), p<0.01), drinking alcohol (AOR (95% CI) = 1.91 (1.51-2.43), p<0.001), having diagnosis of diabetes mellitus (AOR (95% CI) = 1.22 (1.01-1.48), p<0.05), having 1-7 days of self-reported poor physical health (AOR (95% CI) = 1.43 (1.17-1.75), p<0.001) Patients were less likely to be nonadherent to medication if having diagnosis of hypertension (AOR (95% CI) = 0.72 (0.60-0.87), p<0.05), age between 65-74 (AOR (95% CI) = 0.68 (0.55-0.83), p<0.001) and age between 75-84 (AOR (95% CI) = 0.67 (0.53-0.84), p<0.001)

Saqlain *et al*., 2019[44]	n=262, 65+ years M=NA Outpatients with hypertension from tertiary health care centres in Islamabad, Pakistan	SILS	MMAS-4	n=98 (37.4%) patients had adequate HL n=102 (38.9%) patients were adherent to medication	Positive and statistically significant associations between HL and MA (χ^2=24.356, p<0.001) Patients with adequate HL were more likely to be adherent to medication compared to those with inadequate HL (OR (95% CI) = 3.37 (1.91-5.96), p<0.001) Other significant predictors of MA were self-reported good (OR (95% CI) = 4.25 (1.45-12.44), p<0.008) and moderate (OR (95% CI) = 3.54 (1.37-9.16), p<0.009) subjective health and independence in activities of daily living (OR (95% CI) = 2.97 (1.15-5.85), p<0.002)
Seong *et al*., 2019[38]	n=277, 65+ years M=74.2 (7.2) Outpatients with atrial fibrillation undergoing antithrombotic therapy in tertiary general hospital in South Korea	BHLS 3 questions	Single item	HL levels (M=7.9 (3.5)) were inadequate, marginal, and adequate for 28.1%, 45.5%, and 26.4% of patients, respectively n=139 (50.2%) patients were nonadherent to medication Significant differences in MA between age subgroups (p<0.001)	Positive and statistically significant associations between HL and MA (χ^2=22.00, p<0.001) Significant predictive relationship between marginal/ inadequate HL and medication nonadherence in univariate logistic regression analysis (OR (95% CI) = 2.55 (1.29-3.90), p=0.004) but not in multivariate logistic regression analysis (OR (95% CI) = 1.45 (0.79-2.64), p=0.232), where only cognitive impairment was significant predictor for medication nonadherence (OR (95% CI) = 2.63 (1.42-4.85), p=0.002)
Shehadeh-Sheeny *et al*., 2013[45]	n=303, 60+ years M= 71 (6.04) Female Arab patients with osteoporosis from three clinics in Israel	FCCHL	MPR	n=75 (24.8%) patients had high HL compared to n=164 (54.1%) and n=64 (21.1%) with medium and low HL, respectively n=125 (41.3%) patients had high MA	No significant associations between MA and HL (p=0.44) 46.7% of patients with high HL were more adherent to medication compared to 35.9% of patients with low HL In multivariate logistic regression only self-reported income was a significant predictor of MA (OR (95% CI) = 1.26 (1.01-1.58), p=0.037)
Song & Park, 2020[39]	n=116, 65+ years M=72.7 (6.1) Community-dwelling older adults in health care centre, South Korea	BHLS 15 questions	MMAS-8	Mean HL was 42.4 (6.6) Mean MA was at a medium level (M=4.3 (2.2))	HL positively correlated with MA (r=0.42, p<0.001) In multiple regression analysis HL was significant predictor of MA (β=0.23, p<0.001) Other significant predictors of MA were income (β=0.35, p<0.001), number of chronic diseases (β=-0.33, p<0.001), and vision problems (β=-0.32, p<0.001)

Wannasirikul *et al.*, 2016[46]	n=600, 60-70 years M=65.3 Patients with hypertension from primary health care centre in Sa Kaeo Province, Thailand	FCCHL	ARMS	Mean HL was 40.0 (10.4) HL levels were inadequate, marginal, and adequate for 48.7%, 43.8%, and 7.5% of patients, respectively MA was good for 98.3% of patients	SEM supports causal relationship between HL, MA, and blood pressure HL had a significantly positive direct effect on MA in SEM (β=0.08, p<0.05) Cognitive ability ((β=0.22, p<0.05) and literacy (β=0.46, p<0.05) had biggest and significantly positive direct effect on MA Literacy (β=0.15, p<0.05) and cognitive ability (β=0.52, p<0.05) had biggest and significantly positive direct effect on HL HL had biggest significantly negative direct effect on blood pressure level (β=-0.14, p<0.05) MA had a significantly negative direct effect on blood pressure level (β=--0.02, p<0.05) Results suggest mediator effect of HL on MA

Abbreviations: BHLS: Brief Health Literacy Screen, MMAS: Morisky Medication Adherence Scale, HLS-EU-Q: European HL Survey Questionnaire, MOS-SAS: Medical Outcomes Study Specific Adherence Scale, CARDIA: Coronary Artery Risk Development in Young Adults, SILS: Single Item Literacy Screener, FCCHL: Functional, Communicative, and Critical Health Literacy Questionnaire, MPR: Medication Possession Ratio, ARMS: Adherence to Refills and Medications Scale, NA: Not available/ not reported.

DISCUSSION

The aim of this study was to give a systematic overview of the associations between HL and MA in older adults. Although research on HL and MA in older adults has rapidly increased in the last years, mixed results are a common denominator in this area[15 52]. Accordingly, previous systematic reviews resulted in a range of conclusions as they included a variety of HL concepts, different (younger) age groups, and a range of methodologically different instruments (self-reports as well as performance-based measures) to assess HL[12 16 24 26 52]. To our knowledge, this is the first systematic review to focus specifically on self-reported HL while explicitly including studies with samples of older adults. We found that only few validated instruments of self-reported HL are used and that most studies still rely on legacy measures to assess HL even though their use has been criticized repeatedly and self-reports of HL offer a range of advantages[29]. Studies included in our review mostly assessed MA in older adults through self-reports, even though a wide range of tools is known[53 54].

In this review, results appear to be more consistent in contrast to previous reviews[15 16] as many included studies reported positive and statistically significant associations between HL and MA. This could be explained by the fact that only older adults (at least 66% of older adults in samples, not based on the samples´ mean age) were examined in the included studies and associations in this group may be more prominent compared to studies that also include subgroups of younger people. One review[24] for example aimed to review literature that examined HL and MA in older adults with cardiovascular disease or diabetes. Included studies in the review had to assess HL with legacy instruments only and had to include samples of participants with a "[…] mean age [of] at least 50 years or with at least a third of participants aged 50 years or older […]" and could not confirm an association between HL and MA. As stated earlier, inclusion of younger participants may have resulted in unknown bias from age. Yet another bias may have resulted from the utilization of legacy measures with different conceptualizations of HL since the REALM and TOFHLA, two of the most prominent legacy tools of HL, are confirmed to assess different aspects of literacy rather than HL and may thus be differently impacted by a person´s intelligence[29]. Accordingly, Loke *et al*. stated in their review that functional measures of HL may not be adequate and "[n]ew methods of measuring health literacy beyond the functional level are needed […]".

In another review, Ostini *et al*.[16] included studies with samples of all age groups, not disclosing how HL and MA were measured in these studies, and suggested the existence of a U-shaped relationship between HL and nonadherence as patients with high levels of HL may intentionally not adhere while those with low HL levels may unintentionally not adhere. Looking at the included studies in their review, only one study used a self-report measure of HL (BHLS) while all other used one of the performance-based legacy instruments. Since legacy measures of HL rather focus on literacy skills and we could not find any indication of a U-shaped relationship in our review, we want to point out that, while we cannot confirm or rule out a U-shaped relationship between literacy skills and MA, our review might suggest that it does not exist between self-reported HL and MA in older adults. While people with low literacy skills may not be able to understand/read labels/instructions and therefore not adhere (or rather unintentionally not comply) to their medication more often, people with higher literacy skills might read instructions first and subsequently (intentionally) decide not to take their medications due to e.g. possible side effects they read about. However, this phenomenon is not easily transferrable onto other and in some cases broader theoretical concepts of self-reported HL measures (e.g. HLS-EU-Q) since those not only include literacy skills but also other individual skills and situational aspects and may thus show another linear or non-linear association with adherence. Since empirical data on possible associations between literacy and self-

reported HL are still widely lacking, we need more research to explore and develop comprehensive theories in this area.

Six studies[37 38 41 44-46] included in this review found that a majority of participants in the respective samples reported limited (i.e. inadequate, low, marginal) HL. This is consistent with other research that showed that older people commonly reach only low levels of self-reported health literacy[3 25 32] even though this research is very scarce. HL was measured by versions of four different self-reports (BHLS[40 55], HLS-EU-Q[3], SILS[42], FCCHL[43]). This shows that self-reporting HL measures are still rarely utilized when examining older adults, even though the Health literacy Tool Shed[56] lists 29 self-report instruments for HL in English alone (58 without language restrictions).

MA was assessed through self-reports in all but one of the included studies[35-39 41 44 46]. Nevertheless, we recommend a more detailed description of operationalization of MA as many studies still use the concepts of adherence and compliance interchangeably. Interestingly, we had to exclude many studies from this review even though they assessed some form of adherence, because they only included measures of general preventive behaviour (e.g. physical activity) and not MA. However, the use of such secondary adherence measures might be a promising approach to get a more comprehensive picture of adherence in older adults[54]. Especially a multi-method approach could be helpful since self-reported adherence may also be affected by cognitive bias and/or social desirability in older adults. As such, the utilization of both direct (e.g. laboratory measures) and indirect (e.g. self-reports) measures of adherence[54 57] may help to get a better understanding of adherence and its associations with self-reported HL in older adults. A number of studies in this review also included measures of secondary prevention (e.g. physical activity, heart-healthy lifestyle behavior) as well as other factors (e.g. income, cognitive ability) providing further knowledge on possible confounders in the mechanisms between HL and MA. Accordingly, several studies confirmed multiple other factors as predictors for MA (e.g., health status[36 37 44], income[39 45], physical activity[37 44], cognitive ability[38 46]) and/ or HL (e.g., cognitive ability[46], stress management[41]). In a recent systematic review and meta-analysis by Lim et al.[58], the authors examined the associations between physical activity and HL and found that older adults with inadequate levels of HL were "[…] less likely […] to report engaging in physical activity […]" than those with adequate HL, showing the importance of also addressing secondary adherence measures in future research in this area. Notably, their review also included younger adults (samples with mean age ≥55 years) and different of HL measures (legacy measures and self-reports).

Even though we also encourage researchers to assess HL with a multi-method approach (e.g. subjective and objective instruments), we suggest a more rigorous differentiation in analysis and interpretation when comparing HL measures that are based on different concepts (e.g. legacy tools and self-reports). This may also help to clarify further the associations between self-reported HL and literacy as measured by legacy instruments. As stated by Nguyen *et al*.[29], a separation in analyses of objective and subjective measures of HL as well as a closer alignment of HL theory and measurement could help clarify the relationship between HL and MA. This idea was also supported by one of the studies[39] included in this review, which aimed at comparing two different measures of HL (self-report vs. legacy measure). The authors found that even though both measures were significantly and positively correlated to MA, only the self-report was a significant predictor for MA in older adults suggesting that self-reports may be more fitting to access HL when predicting MA since "[…] assessing older adults´ experiences of limited health literacy is more appropriate for catching any decreased medication adherence […]".

This review additionally confirms that age subgroup analyses are conducted very rarely for self-reported HL but quite often for MA. This may result from the fact that research on MA in the elderly is traditionally older than research on HL in the elderly and with regard to HL most studies still treat older people as a homogenous group[25]. Most studies in this review did not find any significant associations between age and MA and only two studies[37 39] reported significant differences in MA between age subgroups. Accordingly, one study[37] reported that young/ young-old people (21-65 years old) were more likely not to adhere to their medication compared to old/older adults (65-84 years old) but not oldest adults (≥85 years old). A second study[39] reported higher MA in 65-69-year-old adults compared to older/oldest adults (70-90 years old). Not surprisingly, only one study conducted analyses on the relationship between age and HL[41], showing that patients with limited HL were significantly older compared to those with adequate HL. Even though generalizability is very limited, these results reveal the necessity for more differentiated analyses (e.g. of subgroups) in future HL and MA research on older adults. In context of demographic change and increasing life expectancy, more differentiated analyses could help to understand specific needs and barriers of elderly (patient) populations with different chronic diseases. Importantly, definitions of *old age* are often inconsistent and include people from ages 60, 65, or 70 years and over. These dissimilarities in the definitions of old age may result from differences in cultural and/or economic standards (e.g. USA vs. Asia) and often manifest in different demographic changes and/or different life expectancies thus resulting in a different quality of health care in groups of older adults. Consequently, when looking at older adults´ health care and health outcomes, it is critical to include contextual aspects such as cultural or economic standards.

Studies in this review show some inconsistencies in the use of cutoffs, use, and wording of HL levels. Of all included studies, six studies[37 38 41 44-46] reported categories of HL (e.g. adequate) of which only three[38 41 44] reported cutoffs for these categories. Three publications[35 36 39] from two studies reported neither categories nor cutoffs for HL and only five publications[35 36 38 39 46] from four studies reported mean values of HL. For example, Shehadeh-Sheeny et al. calculated scores for low, medium, and high levels of HL while Wannasirikul et al. calculated scores for adequate, marginal, and inadequate HL levels even though no cutoffs were reported/available by neither the authors nor the FCCHL measure both studies used. The inconsistent use of cutoffs and wording may indicate a lack of certainty and experience in the application of self-reports enhancing the call for more differentiated research and the development of easy-to-use but still valid tools.

Strength and limitations

The strengths of this study include the exhaustive methodology and comprehensive search strategy that were used. As we followed a strict screening procedure, we are confident that we found all eligible studies. Since we excluded all studies that measured HL with performance-based instruments, we aimed to reduce bias resulting from fundamental differences in constructs and concepts. Although we see this exclusion as a considerable advantage, we cannot eliminate the possibility of bias still resulting from theoretical or practical differences in self-reports as some of them are built on more complex conceptual frameworks than others. Additionally, there are advantages in assessing HL in older adults with self-reports since they reduce the possible bias of performance-based measures resulting from fear of stigma and/or (time)

pressure. Nevertheless, we recognize the inherent limitations of self-reporting tools that may also have biased our results.

Other limitations should be considered. All studies included in this review were cross-sectional, thus we cannot determine any direction of causality. The fair to poor methodological quality of the included studies may also increase the risk of (unknown) bias. Given the heterogeneity of the studies, a meta-analysis (e.g. pooled odds ratios) could not be conducted, thus limiting further understanding of the relationship between HL and MA in older adults. Additionally, our search strategy in this review limited included studies to English and German, which could bias results due to missing research in other languages. Finally, we were not able to include EMBASE as a database in our search. Even though, we are very confident that we did not miss a substantial amount of literature, this must be considered as a limitation of this review.

CONCLUSIONS

In this review, self-reported HL and MA in older adults show a rather straightforward positive association. While previous research on HL and MA in older adults did not always find clear associations, many studies included in this review reported significantly positive associations between HL and MA. In addition, HL plays an important role as a predictor of MA in older adults as several studies in this review could confirm. However, other factors (e.g. cognitive ability) appear equally important in predicting MA in older adults, and future studies should also focus on secondary adherence measures (e.g. physical activity) when examining the associations between HL and MA in the elderly. Finally, study heterogeneity and methodological weaknesses reveal a definitive need for more differentiated research regarding different definitions, concepts, and measures of HL and MA as well as longitudinal research designs and studies that analyse age subgroups in older adults.

Acknowledgements
We would like to thank Dr. rer. biol. hum. Laura Inhestern for her advice during the preparation of the search for this review.

Author Contributions
All authors were involved in the design and planning of the review. MSS prepared, performed, and redefined the searches after consultation with SPH and CB. MSS and SPH performed screening and data extraction with the help of CB in case of disagreements or discussion. All authors contributed to the data analysis and interpretation. MSS wrote the first draft which was critically revised by SPH and CB.

Ethics Approval Statement
This study does not involve human participants, as it is a systematic review.

Funding
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests
None declared.

Patient consent
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data sharing statement
All data relevant to the study are included in the article or uploaded as supplementary information.

REFERENCES

1 United Nations, Department of Economic and Social Affairs, Population Division. World Population Ageing 2019: Highlights (ST/ESA/SER.A/430). 2019.

2 Ratzan SC, Parker RM. Health literacy - identification and response. *J Health Commun* 2006;**11**:713-5.doi:10.1080/10810730601031090

3 Consortium H-E. Comparative Report on Health Literacy in Eight EU Member States. The European Health Literacy Project 2009–2012. Vienna: Ludwig Boltzmann Institute for Health Promotion Research 2012.

4 Berkman ND, Sheridan SL, Donahue KE, et al. Low health literacy and health outcomes: an updated systematic review. *Ann Intern Med* 2011;**155**:97-107.doi:10.7326/0003-4819-155-2-201107190-00005

5 Chesser AK, Keene Woods N, Smothers K, et al. Health Literacy and Older Adults: A Systematic Review. *Gerontol Geriatr Med* 2016;**2**:2333721416630492.doi:10.1177/2333721416630492

6 Vogt D, Schaeffer D, Messer M, et al. Health literacy in old age: results of a German cross-sectional study. *Health Promot Int* 2018;**33**:739-47.doi:10.1093/heapro/dax012

7 Wolf MS, Feinglass J, Thompson J, et al. In search of 'low health literacy': threshold vs. gradient effect of literacy on health status and mortality. *Soc Sci Med* 2010;**70**:1335-41.doi:10.1016/j.socscimed.2009.12.013

8 Gast A, Mathes T. Medication adherence influencing factors—an (updated) overview of systematic reviews. *Systematic Reviews* 2019;**8**:1-17.doi:10.1186/s13643-019-1014-8

9 Hoel RW, Giddings Connolly RM, Takahashi PY. Polypharmacy Management in Older Patients. *Mayo Clinic Proceedings* 2021;**96**:242-56.doi:10.1016/j.mayocp.2020.06.012

10 Chiatti C, Bustacchini S, Furneri G, et al. The economic burden of inappropriate drug prescribing, lack of adherence and compliance, adverse drug events in older people: a systematic review. *Drug Saf* 2012;**35 Suppl 1**:73-87.doi:10.1007/BF03319105

11 Huang YM, Shiyanbola OO, Smith PD. Association of health literacy and medication self-efficacy with medication adherence and diabetes control. *Patient Prefer Adherence* 2018;**12**:793-802.doi:10.2147/PPA.S153312

12 Martins NFF, Abreu DPG, Silva BTD, et al. Functional health literacy and adherence to the medication in older adults: integrative review. *Rev Bras Enferm* 2017;**70**:868-74.doi:10.1590/0034-7167-2016-0625

13 Park NH, Song MS, Shin SY, et al. The effects of medication adherence and health literacy on health-related quality of life in older people with hypertension. *Int J Older People Nurs* 2018;**13**:e12196.doi:10.1111/opn.12196

14 Roh YH, Koh YD, Noh JH, et al. Effect of health literacy on adherence to osteoporosis treatment among patients with distal radius fracture. *Arch Osteoporos* 2017;**12**:42.doi:10.1007/s11657-017-0337-0

15 Zhang NJ, Terry A, McHorney CA. Impact of health literacy on medication adherence: a systematic review and meta-analysis. *Ann Pharmacother* 2014;**48**:741-51.doi:10.1177/1060028014526562

16 Ostini R, Kairuz T. Investigating the association between health literacy and non-adherence. *International journal of clinical pharmacy* 2014;**36**:36-44.doi:10.1007/s11096-013-9895-4

17 Lindquist LA, Go L, Fleisher J, et al. Relationship of health literacy to intentional and unintentional non-adherence of hospital discharge medications. *J Gen Intern Med* 2012;**27**:173-8.doi:10.1007/s11606-011-1886-3

18 Wolf MS, Davis TC, Osborn CY, et al. Literacy, self-efficacy, and HIV medication adherence. *Patient Educ Couns* 2007;**65**:253-60.doi:10.1016/j.pec.2006.08.006

19 Kripalani S, Gatti ME, Jacobson TA. Association of age, health literacy, and medication management strategies with cardiovascular medication adherence. *Patient Educ Couns* 2010;**81**:177-81.doi:10.1016/j.pec.2010.04.030

20 Bauer AM, Schillinger D, Parker MM, et al. Health literacy and antidepressant medication adherence among adults with diabetes: the diabetes study of Northern California (DISTANCE). *J Gen Intern Med* 2013;**28**:1181-7.doi:10.1007/s11606-013-2402-8

21 Mayo-Gamble TL, Mouton C. Examining the Association Between Health Literacy and Medication Adherence Among Older Adults. *Health Commun* 2018;**33**:1124-30.doi:10.1080/10410236.2017.1331311
22 Mosher HJ, Lund BC, Kripalani S, et al. Association of health literacy with medication knowledge, adherence, and adverse drug events among elderly veterans. *J Health Commun* 2012;**17 Suppl 3**:241-51.doi:10.1080/10810730.2012.712611
23 Fang MC, Machtinger EL, Wang F, et al. Health literacy and anticoagulation-related outcomes among patients taking warfarin. *J Gen Intern Med* 2006;**21**:841-6.doi:10.1111/j.1525-1497.2006.00537.x
24 Loke YK, Hinz I, Wang X, et al. Systematic review of consistency between adherence to cardiovascular or diabetes medication and health literacy in older adults. *Ann Pharmacother* 2012;**46**:863-72.doi:10.1345/aph.1Q718
25 Vogt D, Berens EM, Schaeffer D. Gesundheitskompetenz im höheren Lebensalter [Health Literacy in Advanced Age]. *Gesundheitswesen* 2020;**82**:407-12.doi:10.1055/a-0667-8382
26 Geboers B, Brainard JS, Loke YK, et al. The association of health literacy with adherence in older adults, and its role in interventions: a systematic meta-review. *BMC Public Health* 2015;**15**:903.doi:10.1186/s12889-015-2251-y
27 Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened screening instrument. *Fam Med* 1993;**25**:391-5
28 Parker RM, Baker DW, Williams MV, et al. The test of functional health literacy in adults: a new instrument for measuring patients' literacy skills. *J Gen Intern Med* 1995;**10**:537-41.doi:10.1007/BF02640361
29 Nguyen TH, Paasche-Orlow MK, McCormack LA. The state of the science of health literacy measurement. *Information Services & Use* 2017;**37**:189-203.doi:10.3233/ISU-170827
30 Kobayashi LC, Wardle J, Wolf MS, et al. Aging and Functional Health Literacy: A Systematic Review and Meta-Analysis. *J Gerontol B Psychol Sci Soc Sci* 2016;**71**:445-57.doi:10.1093/geronb/gbu161
31 Sørensen K, Van den Broucke S, Pelikan JM, et al. Measuring health literacy in populations: illuminating the design and development process of the European Health Literacy Survey Questionnaire (HLS-EU-Q). *BMC Public Health* 2013;**13**:948.doi:10.1186/1471-2458-13-948
32 Berens EM, Vogt D, Messer M, et al. Health literacy among different age groups in Germany: results of a cross-sectional survey. *BMC Public Health* 2016;**16**:1151.doi:10.1186/s12889-016-3810-6
33 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.doi:10.1371/journal.pmed.1000097
34 National Heart, Lung, and Blood Institute.. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, 2014. Available: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort [Accessed 05 May 2020].
35 Lee SK, Kang BY, Kim HG, et al. Predictors of medication adherence in elderly patients with chronic diseases using support vector machine models. *Healthc Inform Res* 2013;**19**:33-41.doi:10.4258/hir.2013.19.1.33
36 Lee YM, Yu HY, You MA, et al. Impact of health literacy on medication adherence in older people with chronic diseases. *Collegian* 2017;**24**:11-8.doi:10.1016/j.colegn.2015.08.003
37 Reading SR, Black MH, Singer DE, et al. Risk factors for medication non-adherence among atrial fibrillation patients. *BMC Cardiovasc Disord* 2019;**19**:38.doi:10.1186/s12872-019-1019-1
38 Seong HJ, Lee K, Kim BH, et al. Cognitive Impairment Is Independently Associated with Non-Adherence to Antithrombotic Therapy in Older Patients with Atrial Fibrillation. *Int J Environ Res Public Health* 2019;**16**.doi:10.3390/ijerph16152698
39 Song MS, Park S. Comparing two health literacy measurements used for assessing older adults' medication adherence. *J Clin Nurs* 2020;**29**:4313-20.doi:10.1111/jocn.15468
40 Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. *Fam Med* 2004;**36**:588-94

41 Lu M, Ma J, Lin Y, et al. Relationship between patient's health literacy and adherence to coronary heart disease secondary prevention measures. *J Clin Nurs* 2019;**28**:2833-43.doi:10.1111/jocn.14865
42 Morris NS, MacLean CD, Chew LD, et al. The Single Item Literacy Screener: evaluation of a brief instrument to identify limited reading ability. *BMC Fam Pract* 2006;**7**:21.doi:10.1186/1471-2296-7-21
43 Ishikawa H, Takeuchi T, Yano E. Measuring functional, communicative, and critical health literacy among diabetic patients. *Diabetes Care* 2008;**31**:874-9.doi:10.2337/dc07-1932
44 Saqlain M, Riaz A, Malik MN, et al. Medication Adherence and Its Association with Health Literacy and Performance in Activities of Daily Livings among Elderly Hypertensive Patients in Islamabad, Pakistan. *Medicina (Kaunas)* 2019;**55**.doi:10.3390/medicina55050163
45 Shehadeh-Sheeny A, Eilat-Tsanani S, Bishara E, et al. Knowledge and health literacy are not associated with osteoporotic medication adherence, however income is, in Arab postmenopausal women. *Patient Educ Couns* 2013;**93**:282-8.doi:10.1016/j.pec.2013.06.014
46 Wannasirikul P, Termsirikulchai L, Sujirarat D, et al. Health Literacy, Medication Adherence, and Blood Pressure Level among Hypertensive Older Adults Treated at Primary Health Care Centers. *Southeast Asian J Trop Med Public Health* 2016;**47**:109-20
47 Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;**24**:67-74.doi:10.1097/00005650-198601000-00007
48 Sherbourne CD, Hays RD, Ordway L, et al. Antecedents of adherence to medical recommendations: results from the Medical Outcomes Study. *J Behav Med* 1992;**15**:447-68.doi:10.1007/BF00844941
49 Wu JR, DeWalt DA, Baker DW, et al. A single-item self-report medication adherence question predicts hospitalisation and death in patients with heart failure. *J Clin Nurs* 2014;**23**:2554-64.doi:10.1111/jocn.12471
50 Cutter GR, Burke GL, Dyer AR, et al. Cardiovascular risk factors in young adults. The CARDIA baseline monograph. *Control Clin Trials* 1991;**12**:1S-77S.doi:10.1016/0197-2456(91)90002-4
51 Kripalani S, Risser J, Gatti ME, et al. Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients with chronic disease. *Value Health* 2009;**12**:118-23.doi:10.1111/j.1524-4733.2008.00400.x
52 Miller TA. Health literacy and adherence to medical treatment in chronic and acute illness: A meta-analysis. *Patient Educ Couns* 2016;**99**:1079-86.doi:10.1016/j.pec.2016.01.020
53 Lam WY, Fresco P. Medication Adherence Measures: An Overview. *Biomed Res Int* 2015;**2015**:217047.doi:10.1155/2015/217047
54 Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment adherence. *Med Pharm Rep* 2019;**92**:117-22.doi:10.15386/mpr-1201
55 Chew LD, Griffin JM, Partin MR, et al. Validation of screening questions for limited health literacy in a large VA outpatient population. *J Gen Intern Med* 2008;**23**:561-6.doi:10.1007/s11606-008-0520-5
56 Health Literacy Tool Shed, 2020. Available: https://healthliteracy.bu.edu. [Accessed 17 August 2020].
57 McRae-Clark AL, Baker NL, Sonne SC, et al. Concordance of Direct and Indirect Measures of Medication Adherence in A Treatment Trial for Cannabis Dependence. *J Subst Abuse Treat* 2015;**57**:70-4.doi:10.1016/j.jsat.2015.05.002
58 Lim ML, van Schooten KS, Radford KA, et al. Association between health literacy and physical activity in older people: a systematic review and meta-analysis. *Health Promot Int* 2020;**daaa072.**doi:10.1093/heapro/daaa072

Figure 1. PRISMA Flow Diagram
Notes: *no HL measure available (n=184), NVS (n=35), REALM (n=63), TOFHLA (n=90), other performance-based measure (n=5)
**only for samples that not exclusively focus on elders

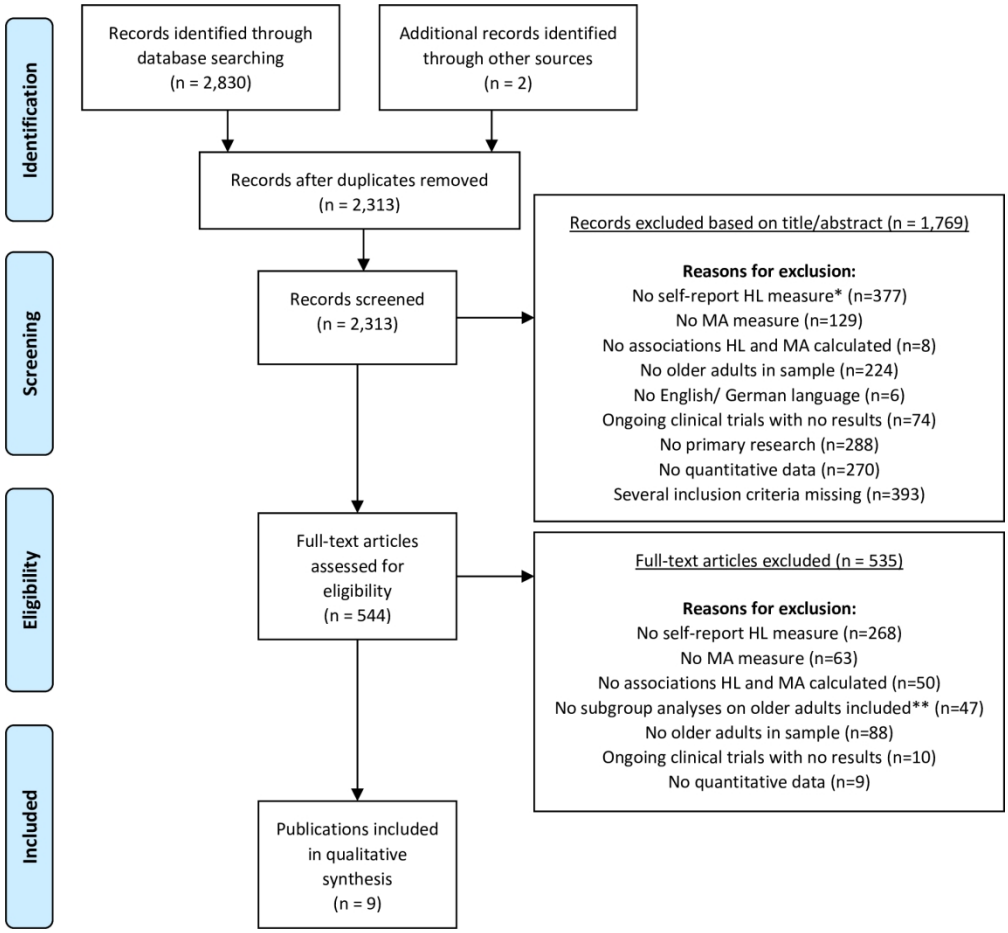

Figure 1. PRISMA Flow Diagram
Notes: *no HL measure available (n=184), NVS (n=35), REALM (n=63), TOFHLA (n=90), other performance-based measure (n=5)
**only for samples that not exclusively focus on elders

168x155mm (300 x 300 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4, Table S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 4-5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 4-5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 5
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Pages 6-14, Tables 1-3 & S3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 6, table S2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 6-14, Tables 1-3 & S3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Table S2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 12-14, Tables 3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 15-17
	23b	Discuss any limitations of the evidence included in the review.	Pages 17-18
	23c	Discuss any limitations of the review processes used.	Page 117-18
	23d	Discuss implications of the results for practice, policy, and future research.	Page 18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4, File S2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	File S2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 19

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	Page 19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Template data collection forms on demand, Pages 4-6, tables 1-3 & S3

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Citation

Moritz Schoenfeld, Stefanie Pfisterer-Heise, Corinna Bergelt. Self-reported health literacy and treatment adherence in older adults: a systematic review. PROSPERO 2019 CRD42019141028 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019141028

Review question

The overall objective of this study is to systematically review all published evidence on the levels and associations of self-reported health literacy and treatment adherence in older adults (over 60 years old).

It specifically aims to:

1. Examine the levels of self-reported health literacy and treatment adherence in (if available, different subgroups of) older adults

2. Evaluate the associations of self-reported health literacy and treatment adherence in older adults

3. Identify how self-reported health literacy and treatment adherence in older adults are measured

4. Investigate moderator and mediator effects of other psychosocial and sociodemographic factors (may include: Quality of life, socioeconomic status, illness perception, physical activity, age, sex)

Searches

A research librarian was consulted for advice on databases prior to the literature search.

The following five electronic databases will be searched:

PubMed, CINAHL, Cochrane Library, Epistemonikos, LIVIVO.

All databases will be searched (adapted searches) from July, 15, 2019 to July 30, 2019. Search was updated in October 2020. Searches will be limited to human subjects.

All eligible literature published until July 2019 will be included (Updated search: October 2020, included as well). Articles must be written in English or German.

In addition, articles will be searched by hand for cross-references. References will be exported to Endnote and duplicates deleted.

Search terms:

"health literacy", "illiteracy", "treatment adherence and compliance", "patient compliance", "compliance", "patient adherence", "adherence", "non-adherence", "nonadherence", "medication adherence", "discontinuation", "non-compliance", "noncompliance", "termination", "refill", "aged", "old", "older", "elderly", geriatric", "oldest", "elders".

Keywords: "health literacy", "adherence", "patient adherence", "patient compliance", "compliance", "aged", "old", "older", "elderly".

Types of study to be included

Primary research (quantitative only, baseline data) will be included. Included study types will be: Randomized controlled trials, prospective and retrospective cohort studies, and cross-sectional studies. Articles must be written in English or German.

Only original, peer-reviewed studies will be included. No systematic reviews, commentaries, conference abstracts, books, meta-analyses or grey literature will be included.

Condition or domain being studied

Levels and associations of self-reported health literacy (subjective measures) and treatment adherence in older (60+ years) adults will be assessed as primary outcomes.

Other psychosocial and sociodemographic factors will be investigated for possible moderator or mediator effects. Currently, there are no reviews that specifically focus on the associations of self-reported (subjective) outcome measures of health literacy and treatment adherence in older adults.

Participants/population

Studies that examined older adults aged 60 years and older will be included. Only studies with at least 2/3 of older adults in samples will be included.

Intervention(s), exposure(s)

Included studies must contain at least one (validated) measure of self-reported health literacy and treatment adherence and must provide at least one measure (e.g. mean) to calculate associations (i.e. correlation, effect size) between health literacy and treatment adherence.

Only studies that assessed health literacy with self-report (subjective) measures will be included. Studies that assessed health literacy with performance-based (objective) tests/ measures will not be included.

Comparator(s)/control

Different baseline levels and associations of health literacy and treatment adherence will be analyzed.

Main outcome(s)

Health literacy (subjective measure only)

Treatment adherence (including medication adherence). Treatment adherence may include pill counts, self-reports, questionnaires, screeners, and refill records.

Measures of effect

Baseline.

Additional outcome(s)

None.

Measures of effect

Not applicable.

Data extraction (selection and coding)

All search results will be exported to Endnote X8 reference management software and screened for duplicates.

Titles and abstract will be screened by two reviewers independently using a standardized checklist that will be developed for this purpose. Both reviewers will then assess full-text articles for eligibility based on clearly stated criteria. Cases of missing consensus will be discussed and, if necessary, resolved by a third reviewer. Inclusion and exclusion of all studies will be documented and presented according to PRISMA guidelines.

A data extraction sheet for data extraction from eligible studies will be developed and pilot tested, and data will be documented in Microsoft Excel.

Data extraction will include the following criteria: Title, authors, year published, journal title, assessment of health literacy and treatment adherence, psychosocial and sociodemographic outcomes with moderator and mediator effects, statistical measures to calculate associations between health literacy and treatment adherence, population and setting details, sample size, age groups, statistical significance if available.

Risk of bias (quality) assessment

Quality assessment of included full-text studies will be conducted by both reviewers using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

The NIH was deemed appropriate, since only baseline data (levels and associations of health literacy and treatment adherence) will be analyzed.

Strategy for data synthesis

Data synthesis will be conducted in accordance to PRISMA guidelines (Liberati et al., 2009).

Since only studies with subjective measures of health literacy will be included, high heterogeneity (e.g. different measures of health literacy and treatment adherence) is expected. Accordingly, a narrative synthesis will be conducted to summarize the studies thematically.

Analysis of subgroups or subsets

If available, subgroup analyses of the levels and associations of health literacy and treatment adherence in different age groups (e.g. 60-64, 65-69, 70-74, 75-79, over 80) will be conducted.

Contact details for further information

Moritz Schoenfeld
mo.schoenfeld@uke.de

Organisational affiliation of the review

University Medical Center Hamburg-Eppendorf, Department of Medical Psychology

https://www.uke.de/kliniken-institute/institute/institut-und-poliklinik-f%C3%BCr-medizinische-psychologie/index.html

Review team members and their organisational affiliations

Mr Moritz Schoenfeld. University Medical Center Hamburg-Eppendorf, Department of Medical Psychology
Mrs Stefanie Pfisterer-Heise. University Medical Center Hamburg-Eppendorf, Department of Biochemistry and Molecular Cell Biology
Professor Corinna Bergelt. University Medical Center Hamburg-Eppendorf, Deparment of Medical Psychology

Type and method of review

Narrative synthesis, Systematic review

Anticipated or actual start date

01 May 2019

Anticipated completion date

30 September 2020

Funding sources/sponsors

None.

Conflicts of interest

Language

English

Country

Germany

Stage of review

Review Completed not published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Health Literacy; Humans; Medication Adherence; Self Report

Date of registration in PROSPERO

24 October 2019

Date of first submission

12 July 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Search was updated in October 2020 and slightly adapted to possibly include newer and relevant literature. Age inclusion criteria were slightly adapted to include studies with (at least 2/3 of) participants 60 years and older, since we noticed some dissimilarities in definitions of "old age" in the studies found in our preliminary search, and decided to also include those studies as they appeared relevant to our research question.The review is now being prepared for dissemination and publication.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

24 October 2019
13 October 2020
10 March 2021

Table S1. Search strategy used in different databases	
Source of search	Search terms
PubMed (MEDLINE)	(health literacy OR illiteracy) AND (treatment adherence and compliance OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR nonadherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR termination OR refill) AND (aged OR old OR older OR elderly OR geriatric OR oldest OR elders)
CINAHL	(health literacy OR illiteracy) AND (treatment adherence and compliance OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR nonadherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR termination OR refill) AND (aged OR old OR older OR elderly OR geriatric OR oldest OR elders)
COCHRANE	health literacy OR illiteracy in Title Abstract Keyword AND treatment adherence OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR nonadherence OR termination OR refill in Title Abstract Keyword AND aged OR old OR older OR elderly OR geriatric OR oldest OR elders in Title Abstract Keyword - (Word variations have been searched)
LIVIVO	("health literacy") AND ("patient compliance and compliance" OR "patient adherence" OR adherence) AND (aged OR old OR older OR elderly)
Epistemonikos	(advanced_title_en:(health literacy OR illiteracy) OR advanced_abstract_en:(health literacy OR illiteracy)) AND (advanced_title_en:(treatment adherence OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR nonadherence OR termination OR refill) OR advanced_abstract_en:(patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR nonadherence OR termination OR refill)) AND (advanced_title_en:(aged OR old OR older OR elderly OR geriatric OR oldest OR elders) OR advanced_abstract_en:(aged OR old OR older OR elderly OR geriatric OR oldest OR elders)) [Filters: protocol=no]

PubMed Search

Search: **(health literacy OR illiteracy) AND (treatment adherence and compliance OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR nonadherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR termination OR refill) AND (aged OR old OR older OR elderly OR geriatric OR oldest OR elders)**

("health literacy"[MeSH Terms] OR ("health"[All Fields] AND "literacy"[All Fields]) OR "health literacy"[All Fields] OR ("literacy"[MeSH Terms] OR "literacy"[All Fields] OR "illiteracy"[All Fields])) AND ("treatment adherence and compliance"[MeSH Terms] OR ("treatment"[All Fields] AND "adherence"[All Fields] AND "compliance"[All Fields]) OR "treatment adherence and compliance"[All Fields] OR ("patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields]) OR ("compliances"[All Fields] OR "patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "compliance"[All Fields] OR "compliance"[MeSH Terms]) OR ("patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR ("patient"[All Fields] AND "adherence"[All Fields]) OR

"patient adherence"[All Fields]) OR ("adherance"[All Fields] OR "adhere"[All Fields] OR "adhered"[All Fields] OR "adherence"[All Fields] OR "adherences"[All Fields] OR "adherent"[All Fields] OR "adherents"[All Fields] OR "adherer"[All Fields] OR "adherers"[All Fields] OR "adheres"[All Fields] OR "adhering"[All Fields]) OR "non-adherence"[All Fields] OR ("nonadherence"[All Fields] OR "nonadherent"[All Fields] OR "nonadherents"[All Fields] OR "nonadherers"[All Fields]) OR ("medication adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "medication adherence"[All Fields]) OR ("discontinuance"[All Fields] OR "discontinuances"[All Fields] OR "discontinuated"[All Fields] OR "discontinuation"[All Fields] OR "discontinuations"[All Fields] OR "discontinue"[All Fields] OR "discontinued"[All Fields] OR "discontinuer"[All Fields] OR "discontinuers"[All Fields] OR "discontinues"[All Fields] OR "discontinuing"[All Fields]) OR "non-compliance"[All Fields] OR ("noncompliant"[All Fields] OR "noncompliants"[All Fields] OR "noncompliers"[All Fields] OR "noncomplying"[All Fields] OR "patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "noncompliance"[All Fields] OR "noncompliances"[All Fields]) OR ("terminal"[All Fields] OR "terminal s"[All Fields] OR "terminally"[All Fields] OR "terminals"[All Fields] OR "terminate"[All Fields] OR "terminated"[All Fields] OR "terminates"[All Fields] OR "terminating"[All Fields] OR "termination"[All Fields] OR "terminations"[All Fields] OR "terminator"[All Fields] OR "terminators"[All Fields]) OR ("refill"[All Fields] OR "refillable"[All Fields] OR "refilled"[All Fields] OR "refilling"[All Fields] OR "refills"[All Fields])) AND ("aged"[MeSH Terms] OR "aged"[All Fields] OR "old"[All Fields] OR ("older"[All Fields] OR "olders"[All Fields]) OR ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("geriatric"[All Fields] OR "geriatrics"[MeSH Terms] OR "geriatrics"[All Fields]) OR "oldest"[All Fields] OR ("elder s"[All Fields] OR "elders"[All Fields] OR "sambucus"[MeSH Terms] OR "sambucus"[All Fields] OR "elder"[All Fields]))

Table S2. Risk of Bias of reviewed studies based on NHLBI

Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total[1]
Lee et al., 2013	+	+	NR	+	-	-	-	+	+	-	+	-	NA	+	fair
Lee et al., 2017	+	+	+	+	+	-	-	-	+	-	+	-	NA	+	fair
Lu et al., 2019	+	+	+	+	+	-	-	-	+	-	+	NR	NA	+	fair
Reading et al., 2019	+	+	+	+	-	-	-	+	-	-	-	NR	NA	+	poor
Saqlain et al., 2019	+	+	+	+	+	-	-	+	+	-	+	-	NA	+	fair
Seong et al., 2019	+	+	NR	+	+	-	-	+	+	-	+	NR	NA	+	fair
Shehadeh-Sheeny et al., 2013	+	+	+	+	-	-	-	+	+	-	+	-	NA	+	fair
Song & Park, 2020	+	+	+	+	+	-	-	-	+	-	+	NR	NA	+	fair
Wannasirikul et al., 2016	+	+	+	+	+	-	-	+	+	-	+	-	NA	+	fair

Notes and abbreviations: [1]Total scores were calculated based on the single scores and a critical appraisal of the methodological quality of each study in accordance with the NHLBI.

NR: Not relevant, NA/NR: Not available/not reported.

Criteria: 1. Was the research question or objective in this paper clearly stated?; 2. Was the study population clearly specified and defined?; 3. Was the participation rate of eligible persons at least 50%?; 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?; 5. Was a sample size justification, power description, or variance and effect estimates provided?; 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?; 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?; 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?; 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; 10. Was the exposure(s) assessed more than once over time?; 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; 12. Were the outcome assessors blinded to the exposure status of participants?; 13. Was loss to follow-up after baseline 20% or less?; 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?.

The NHLBI can be found in: National Heart, Lung, and Blood Institute. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. 2014. Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort.

Table S3. Cutoffs and categorization of measures of health literacy and medication adherence

Authors, year	HL measures	Reported range and cutoff/ categories of HL scores	MA measure	Reported range and cutoff/ categories of MA scores
Lee *et al.*, 2013	BHLS 3 questions	Range of overall HL scores: 3-15 with higher scores indicating higher HL Cutoff/ categories: NA	MMAS-4	Range of overall MA scores: 0-4 with higher scores indicating higher MA Cutoff/ categories: MA scores were dichotomized into nonadherence (scores ≤ 2) and adherence (scores ≥3)
Lee *et al.*, 2017	BHLS 15 questions	Range of overall HL scores: 15-75 with higher scores indicating higher HL Cutoff/ categories: NA	MMAS-8	Range of overall MA scores: 0-8 with higher scores indicating higher MA Cutoff/ categories: Scores were categorized into high (scores of 8), medium (scores 6-7), and low (scores ≤5) MA
Lu *et al.*, 2019	HLS-EU-Q16	Range of overall HL scores: 0-50 with higher scores indicating higher HL Cutoff/ categories: Scores ≤33 indicated limited HL, scores >34 indicated adequate HL	MOS-SAS	Range of MA scores: 0-5 with higher scores indicating higher MA Cutoff/ categories: Scores were dichotomized into adherence (scores ≥4) and nonadherence (scores ≥3)
Reading *et al.*, 2019	BHLS 3 questions	Range of overall HL scores: 3-15 with higher scores indicating higher HL Cutoff/ categories: HL was dichotomized into adequate and inadequate, but no cutoffs were reported	CARDIA (3 questions)	Range of MA scores: NA Cutoff/ categories: Nonadherence was defined according to scale for each answer (1. answers "75% of the time" or less; 2. /3. answers "once per week" or more)
Saqlain *et al.*, 2019	SILS	Range of overall HL scores: 1-5 with higher scores indicating lower HL Cutoff/ categories: HL scores ≥3 indicated inadequate HL and scores ≤2 indicated adequate HL	MMAS-4	Range of overall MA scores: 0-4 with higher scores indicating higher MA Cutoff/ categories: MA scores were dichotomized into nonadherence (scores ≤ 3) and adherence (scores of 4)
Seong *et al.*, 2019	BHLS 3 questions	Range of overall HL scores: 0-12 with higher scores indicating higher HL Cutoff/ categories: HL scores were categorized into inadequate (scores ≤6), marginal (scores 7-10), and adequate (scores 11-12) HL	Single item ("In the past week, have you forgotten to take your antithrombotic medication for various reasons?")	Range of overall MA scores: 1-5 with higher scores indicating higher MA Cutoff/ categories: MA scores were dichotomized into nonadherence (scores ≤ 5) and adherence (scores of 6)
Shehadeh-Sheeny *et al.*, 2013	FCCHL	Range of overall HL scores: NA, higher scores indicating higher HL Cutoff/ categories: HL scores were categorized into low, medium, and high HL, but no cut offs were reported/ are available	MPR	Range of overall MA scores: 0-1 (0%-100%), higher scores indicating higher MA Cutoff/ categories: MA scores were categorized into low (MPR ≤ 0.2) and high (MPR ≥ 0.8) MA

Song & Park, 2020	BHLS 15 questions	Range of overall HL scores: 15-75 with higher scores indicating higher HL Cutoff/ categories: NA	MMAS-8	Range of overall MA scores: 0-8 with higher scores indicating higher MA Cutoff/ categories: NA
Wannasirikul *et al*., 2016	FCCHL	Range of overall HL scores: 17-68 with higher scores indicating higher HL Cutoff/ categories: HL scores were categorized into inadequate, marginal, and adequate HL, but no cut offs were reported/ are available	ARMS	Range of overall MA scores: 14-56 with higher scores indicating higher MA Cutoff/ categories: NA

Abbreviations: HL: Health literacy, MA: Medication Adherence, BHLS: Brief Health Literacy Screen, MMAS: Morisky Medication Adherence Scale, HLS-EU-Q: European Health Literacy Survey Questionnaire, MOS-SAS: Medical Outcomes Study Specific Adherence Scale, CARDIA: Coronary Artery Risk Development in Young Adults, SILS: Single Item Literacy Screener, FCCHL: Functional, Communicative, and Critical Health Literacy Questionnaire, MPR: Medication Possession Ratio, ARMS: Adherence to Refills and Medications Scale, NA: Not available/ not reported.

BMJ Open

Self-reported health literacy and medication adherence in older adults: A systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-056307.R2
Article Type:	Original research
Date Submitted by the Author:	10-Nov-2021
Complete List of Authors:	Schönfeld, Moritz; University Medical Center Hamburg-Eppendorf, Department of Medical Psychology Pfisterer-Heise, Stefanie; University Medical Center Hamburg-Eppendorf, Department of Biochemistry and Molecular Cell Biology Bergelt, Corinna; University Medical Center Hamburg-Eppendorf, Department of Medical Psychology; University Medicine Greifswald, Institute of Medical Psychology
Primary Subject Heading:	Public health
Secondary Subject Heading:	Geriatric medicine, Research methods
Keywords:	PUBLIC HEALTH, GERIATRIC MEDICINE, STATISTICS & RESEARCH METHODS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Self-reported health literacy and medication adherence in older adults: A systematic review

Schönfeld MS[1], Pfisterer-Heise S[2], Bergelt C[1,3]

[1] Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
[2] Department of Biochemistry and Molecular Cell Biology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
[3] Department of Medical Psychology, University Medicine Greifswald, Greifswald, Germany

Corresponding author:
Moritz Sebastian Schönfeld
University Medical Centre Hamburg-Eppendorf
Department of Medical Psychology
Martinistrasse 52
20246 Hamburg
Germany
mo.schoenfeld@uke.de
Tel: +49-40-7410-59140

Word count
5529 words

Date and version
First submission of manuscript: October 29, 2020
1. Resubmission of revised manuscript: August 10, 2021
2. Resubmission of revised manuscript: August 26, 2021
3. Resubmission of revised manuscript: October 1, 2021
4. Resubmission of revised manuscript: November 10, 2021

Abstract

Objectives. To give an overview over the associations between self-reported health literacy and medication adherence in older adults.

Design A systematic literature review of quantitative studies published in English and German.

Data sources. MEDLINE via PubMed, CINAHL, Cochrane Library, Epistemonikos, and LIVIVO were searched.

Eligibility criteria. Included studies had to examine the associations between self-reported health literacy and medication adherence in the elderly (samples including ≥66% of ≥60 years old), had to use a quantitative methodology and had to be written in English or German.

Data extraction and synthesis. All studies were screened for inclusion criteria by two independent reviewers. A narrative synthesis was applied to analyse all included studies thematically. Quality assessment was conducted using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI).

Results. We found 2,313 studies of which nine publications from eight studies were included in this review. Five studies reported a majority of participants with limited health literacy, one study reported a majority of participants with adequate health literacy, and three publications from two studies only reported mean levels of health literacy. Eight publications from seven studies used self-reports to measure medication adherence, while one study used the medication possession ratio. Overall, six publications from five studies reported significantly positive associations between health literacy and medication adherence while two studies reported positive but nonsignificant associations between both constructs and one study reported mixed results.

Conclusion. In this review, associations between self-reported health literacy and medication adherence are rather consistent indicating positive associations between both constructs in older adults. However, concepts and measures of health literacy and medication adherence applied in the included studies still show a noteworthy amount of heterogeneity (e.g. different use of cutoffs). These results reveal the need for more differentiated research in this area.

PROSPERO registration number. CRD42019141028.

Strengths and limitations of this study

- To our knowledge, this is the first systematic review to specifically give an overview of existing literature on the association between self-reported health literacy and medication adherence in older adults.
- The review protocol was registered prospectively, and the review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
- Overall, the included studies showed a considerable level of heterogeneity, and the quality of the included studies was predominantly fair, which is a limitation of this review.
- Health literacy is still commonly assessed with performance-based measures, making literature searches for self-reports in this field challenging.

INTRODUCTION

Within the last decades, demographic change and increasing life expectancy have put older adults (≥60 years old as defined by the United Nations[1]) in the focus of health care research. With increasing age, the risk of chronic diseases and comorbidities rises resulting in a growing number of necessary treatments (e.g. medication), and adherence to these treatments becomes crucial to reduce adverse reactions and ensure safe and effective care. In this context, health literacy (HL), often defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions"[2], has been identified as a key influencing factor of improving health-related behaviour in the elderly[3]. Accordingly, (elderly) people with low levels of HL use health care more often and show higher rates of hospitalization than those with high levels of HL[3 4].

Research also confirmed low HL as a predictor of poor health outcomes linking lower HL to higher age[5 6], lower income[5] and lower education[3 7]. In addition, HL has been repeatedly linked to medication adherence, commonly defined as "the extent to which a patient's behaviour corresponds with the prescribed medication dosing regime, including time, dosing and interval of medication intake"[8]. Medication adherence (MA) has been the focus of this research since the number of medications taken commonly increases with increasing age, making medication the most common form of therapy in the elderly, often resulting in polypharmacy[9 10]. Thus, MA still plays a crucial role in the elderly patient´s care. However, research into the associations between HL and MA stays inconclusive[11-16]. While multiple studies report (significantly) positive associations between HL and MA[17-21], others report (significantly) negative associations[22 23].

Systematic reviews specifically conducted to analyse the relationship between HL and MA in the elderly resulted in mixed findings as they often included studies with a variety of populations and measures of HL[12 16 24]. Older adults have commonly been examined as a homogenous group not taking into account possible differences in levels of HL and MA between subgroups of age (e.g. 65-70 years old, 71-75 years old, 76-80 years old, 85+ years old[6 25]). In addition, reviews and meta-analyses examining the associations between HL and MA in older age commonly included samples with a wide age range only focusing on the mean age of samples. Since these samples often include (undisclosed) proportions of younger adults and subgroups are not reported, results may not adequately reflect the relationship between HL and MA in older adults[24 26]. Previous reviews commonly aimed to include a wide selection of validated measures of HL. However, since only a low proportion of relevant studies are measuring HL with self-reports, these reviews often resulted in a focus on the so-called legacy instruments of HL (i.e. REALM[27], TOFHLA[28])[12 24] and thus included different measures and concepts of HL, which may have led to unknown bias[15 26]. As recently stated by Nguyen *et al*.[29], these often-deployed legacy tools may measure different aspects of literacy and may not be appropriate to assess HL in older adults. Accordingly, limited HL was found to be strongly associated with older age when measured with the TOFHLA (mainly assessing reading, comprehension and numeracy skills[28]) while limited HL had weak associations with older age[30] when measured with the REALM (mainly assessing medical vocabulary[27]).

As of late, these methodological shortcomings in research into HL have been increasingly recognized leading to a broader discussion about the conceptualization and measurement of HL. Most recently, researchers started concentrating on self-report measures of HL as new questionnaires from more comprehensive concepts were developed (e.g. the HLS-EU-Q[31]). Compared to performance-based measures, self-reports of HL commonly offer a fast, easy, and inexpensive way to collect data and have a lower risk of stigma[29]. Accordingly, self-reports present important advantages when assessing HL in

different populations and contexts as they can be applied more effortless. More recently, some studies began to investigate levels of HL in different subgroups of older age resulting in a renewed call for more differentiated methods and analyses in this population[25 32].

Thus, our review aims to systematically review the evidence on self-reported HL and MA in older adults (≥60 years old) including: 1. the levels of self-reported HL and MA (if available, levels of different subgroups); 2. the associations between self-reported HL and MA; 3. how self-reported HL and MA are measured; and (if available) 4. moderator and mediator effects of other psychosocial factors.

METHODS

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[33]. A checklist of PRISMA items can be found in online supplementary file S1. This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42019141028. The protocol is presented in online supplementary file S2.

Eligibility criteria

Population. Studies examining elderly adults aged 60 years and older were included. In case of study samples with a wider age range, only studies with ≥66% of participants 60 years and older were included to ensure only including studies with a majority of older adults.

Intervention. No specific interventions were included in the criteria. Nevertheless, only studies that assessed associations (e.g. correlation, effect size) between self-reported HL and MA were deemed eligible. Studies that assessed HL solely with a performance-based test instrument (e.g. REALM[27], TOFHLA[28]) were excluded from this review.

Outcomes. Studies examining HL with a validated self-report (subjective measure) as well as MA (measured by e.g. questionnaires, refill records) were included.

Study design. Only primary quantitative research (RCTs, prospective and retrospective cohort studies, and cross-sectional studies) published in English or German was included. In case of multiple time-points, only baseline data was included to ensure comparability.

Data sources and search strategy

An electronic search was performed in five electronic databases (MEDLINE via PubMed (1984-2021), CINAHL (1995-2021), Cochrane Library (1997-2021), Epistemonikos (1995-2021), LIVIVO (1966-2021)) between July 15 and July 30, 2019 by the first author and updated again in July 2021. The search was not limited to a specific time frame. A comprehensive search strategy was applied using combinations of the following search terms: “Health literacy", “illiteracy”, “treatment adherence and compliance”, “patient compliance”, “compliance”, “patient adherence” “adherence”, “non-adherence”, “nonadherence”, “medication adherence”, “discontinuation”, “non-compliance”, “noncompliance”, “termination”, “refill”, "aged”, “old”, “older”, “elderly”, “geriatric”, “oldest”, “elders”. As these databases use partially different search algorithms, the search strategy was adapted using MeSH-Terms and Boolean operators (“AND”, “OR”) if applicable (online supplementary table S1). Although this systematic review focuses on self-reports of HL, the terms “self-report” or “subjective” were not included for reasons of higher sensitivity.

In addition, reference lists from eligible articles were hand searched accordingly. All references were subsequently imported into Endnote X8 reference management software for screening purposes.

Study selection and screening

After removal of duplicates, two raters (MSS, SPH) screened titles and abstracts of all remaining studies for eligibility. A checklist was developed for this purpose which included a list of inclusion and exclusion criteria, such as type of measure of HL, MA, and included sample, to allow for a careful screening process. As many studies include HL only as a secondary outcome and may thus not state it in the study's title or abstract, a more liberal title/ abstract screening was conducted. Accordingly, two raters (MSS, SPH) assessed the full texts of all previously screened studies independently. Figure 1 shows specific reasons for study exclusion, which included lack of self-report HL measure, lack of MA measure, lack of associations between HL and MA, lack of older adults in sample, lack of English or German language, being an ongoing clinical trial with no results, lack of primary research (e.g. book chapter), lack of quantitative data (e.g. interview study), or several of these reasons. In case of discrepancies, conflicts were discussed until consensus was reached.

Quality assessment

The methodological quality of all studies included in this review was assessed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, NIH[34]). Since only baseline data from quantitative research was included, the NHLBI was deemed appropriate. The NHLBI contains 14 criteria mainly to assess the internal validity of a study. Each item was answered "yes" (if criterion was met), "no" (if criterion was not met) or "cannot determine/ not applicable/ not reported". As the NHLBI is not meant to assess the study quality by simply summing up its scores, an overall quality rating ("good", "fair", "poor") for each study included a comprehensive and critical appraisal of each criterion as well as the study as a whole. This included e.g. the number of participants, the precision of the findings, and the risk of bias of the included studies.

Data extraction and synthesis

All relevant data was extracted by the first author with the help of a data extraction checklist that was developed for this purpose and contained the following information about each included study: title, authors, year published, study design and setting, sample and sample size, age subgroups, definition and assessment of HL and MA, moderator and mediator effects (if available), statistical measures to calculate associations between HL and MA (e.g. correlation), statistical significance if available.

As the studies showed heterogeneity due to differences in study design, participants, risk of bias, and operationalization of HL and MA (e.g. different use of cutoffs and levels of HL), a narrative synthesis was applied to analyse the studies thematically.

Patient and public involvement

Patients or the public were not involved in this study.

RESULTS

Search results

The literature search resulted in a total of 2,313 studies after removal of duplicates. After screening for title and abstract another 1,769 studies were excluded based on exclusion criteria (figure 1). Full texts of 544 studies were screened and nine publications from eight studies met all eligibility criteria and were thus included in this review (figure 1). The main reason for study exclusion in the screening process was lack of self-reports of HL measure.

Study characteristics

Overall study characteristics are presented in table 1. All included publications were published between 2013 and 2020 with sample sizes between n=116 and n=12,159 (Median=293). The proportion of female participants ranged from 33% to 100% (Median=53.6%). All studies adopted a cross-sectional design (5 survey studies). Three studies (four publications) were conducted in South Korea, and one study each in China, USA, Pakistan, Israel, and Thailand. Studies were conducted across settings of tertiary care hospitals (n=5), primary health care (n=1), private health care centres (n=1), community health care centres (n=1), and clinics (n=1). All studies examined patients/adults with different types of (chronic) diseases: hypertension (n=2), heart diseases (n=1), atrial fibrillation (n=2), osteoporosis (n=1), several chronic diseases (n=3). Due to eligibility criteria restricting included samples to those with ≥66% of older adults (60 years of age and older), all studies focused on the elderly and only two studies also included patients younger than 60 years (table 1). Five studies included samples with a higher proportion of women.

Quality assessment

Study quality in terms of methodological quality and risk of bias was considered poor for one publication and fair for eight publications (online supplementary table S2). In most cases, low study quality occurred from lack of randomization, blinding, and longitudinal data. Accordingly, results in this review should be interpreted with caution.

Health literacy – key findings

In five publications from four studies[35-39] self-reported HL was measured using a selection of questions from the Brief Health Literacy Screen (BHLS[40]). The BHLS employs three to fifteen questions (e.g. “How often do you have someone help you read hospital materials?”) to identify people with inadequate levels of HL. Another study[41] used the short version of the European Health Literacy Survey Questionnaire (HLS-EU-Q) which was designed by the HLS-EU-Consortium based on a conceptual framework of HL[31]. One study assessed HL with the Single Item Literacy Screener (SILS), which asks ““How often do you need to have someone help when you read instructions, pamphlets, or other written material from your doctor or pharmacy?”[42]. Another two studies adopted the Functional, Communicative, and Critical Health Literacy questionnaire (FCCHL) developed by Ishikawa *et al*.[43], a validated questionnaire that assesses three areas of HL: functional HL, communicative HL, and critical HL.

Results on the overall levels of HL were mixed, yet a tendency towards limited HL (i.e. marginal, low, inadequate) in the elderly was observable. While three publications from two studies[35 36 39] only reported mean levels of HL in samples patients aged 65 years and older, six studies reported different levels of HL (e.g. marginal, low, or adequate HL). Three of these six studies[38 41 44] used cutoffs recommended by the original authors of the assessment instruments whereas three studies[37 45 46] did not report how they

calculated HL scores. Five of these six studies[38 41 44-46] found that a majority of the respective samples reported limited HL levels (i.e. more people had low scores of HL; range from 62.6% to 92.5%, Median=74.5%) whereas one study[37] found that a majority of the sample reported adequate levels of HL (i.e. more people had high scores of HL; 76.9%).

Medication adherence – key findings

Four publications from three studies[35 36 39 44] employed versions of the Morisky Medication Adherence Scale (MMAS[47]) to assess MA. The MMAS consists of four to eight questions asking about different aspects of medication intake behaviour (e.g. "Do you sometimes forget to take your medication?"[47]). One study[41] used the Medical Outcomes Study Specific Adherence Scale (MOS-SAS[48]) which addresses MA ("How often have you done each of the following in the past 4 weeks: Took medication as prescribed (on time without skipping dosis)?") as well as heart-healthy lifestyle behaviour (i.e. six preventive behaviours for coronary heart disease, e.g. low-salt diet). One study[38] used a single-item adopted from Wu *et al*.[49] to assess MA ("In the past week, have you forgotten to take your antithrombotic medication for various reasons?"). Another study[37] adopted three questions from the Coronary Artery Risk Development in Young Adults (CARDIA[50]) to assess MA (1. "In the past month, how often did you take your medications as the doctor prescribed?"; 2. "In the past month, how often did you forget to take 1 or more of your prescribed medications?"; 3. "In the past month, how often did you decide to skip 1 or more of your prescribed medications?"). MA was also assessed by the Medication Possession Ratio (MPR) in one study[45]. The MPR commonly represents the period during which a patient has an adequate amount of supply of his/her medication available over a predefined amount of time (e.g. a year). One study assessed MA with the Adherence to Refills and Medication Scale (ARMS[51]) which assesses if a patient can correctly take and refill his or her medication on schedule.

Overall, five publications from four studies[35 36 38 44 45] found that a majority of the sample reported low levels of MA (i.e. more non-adherers; range from 50.2% to 69.4%, Median=59.0%) while three studies[37 41 46] in contrast, found that a majority of the sample reported high levels of MA (i.e. more adherers; range from 84.7% to 98.3%, Median=93.7%). One study reported a sample mean score of MA only[39].

Table 1. Overall summary of included studies

Authors, year	Setting, country	Sample					Methodological quality[1]
		N	Age (years), mean (±SD)	% Female	Age subgroups	Disease	
Lee *et al.*, 2013[35]	Tertiary care hospitals, South Korea	n=293	65+ M=74.4 (6.3)	46.8%	NA	Chronic Diseases	fair
Lee *et al.*, 2017[36]	Tertiary care hospital, South Korea	n=291	65+ M=NA	53.6%	65-74 (57.0%) ≥75 (43.0%)	Chronic Diseases	fair
Lu *et al.*, 2019[41]	Tertiary care hospital, China	n=598	M=65.8 (9.4)	33.3%	≤60 (21.5%) 61-70 (43.0%) 71-80 (29.7%) ≥81 (5.7%)	Coronary Heart Disease	fair
Reading *et al.*, 2019[37]	Private care centres, USA	n=12159	21+ 72.7 (64.4-79.9†, adherent patients) 70.1 (59.5-79.1†, nonadherent patients)	43.0%	<65 (27.2%) 65-74 (30.8%) 75-84 (30.5%) ≥85 (11.5%)	Atrial Fibrillation	poor
Saqlain *et al.*, 2019[44]	Tertiary care centres, Pakistan	n=262	65+ M=NA	64.5%	65-75 (84.7%) 76-85 (11.1%) >85 (4.2%)	Hypertension	fair
Seong *et al.*, 2019[38]	Tertiary general hospital, South Korea	n=277	65+ M=74.2 (7.2)	40.8%	65-70 (32.1%) 70-79 (45.5%) ≥80 (22.4%)	Atrial Fibrillation	fair
Shehadeh-Sheeny *et al.*, 2013[45]	Clinics, Israel	n=303	60+ M=71 (6.04)	100%	60-65 (21.5%) 66-75 (54.1%) 76-85 (24.4%)	Osteoporosis	fair
Song & Park, 2020[39]	Community Health Centre, South Korea	n=116	65+ M=72.7 (6.1)	69.8%	65-69 (38.8%) 70-79 (43.1%) ≥80 (18.1%)	Chronic Diseases	fair
Wannasirikul *et al.*, 2016[46]	Primary Care Centre, Thailand	n=600	60-70 M=65.3 (NA)	75.8%	60-65 (52.7%) 66-70 (47.3%)	Hypertension	fair

Notes and abbreviations. † Median (Interquartile range).[1] Methodological quality of studies was measured using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, NIH[34], further details can be found in online supplementary table S2). NA: Not available/ not reported.

Age subgroups – key findings

Seven studies[36-39 41 44 45] included in this review examined age subgroups for differences in HL and/or MA. All of these studies conducted subgroup analyses for differences in MA while only one of these studies[41] examined differences in HL between age subgroups (e.g. 65-75 years old, 76-85 years old, >85 years old; table 2).

Overall, four studies[36 41 44 45] found no significant differences in MA between age subgroups while one study[37] reported age as a significant predictor of medication nonadherence as younger patients (<65 years old) were more likely to be nonadherent compared to old/older patients (age groups 65-74 years old and 75-84 years old) but not compared to the oldest (≥85 years old). One study[39] reported higher MA in 65-69-year-old adults compared to 70-79-year-old adults and ≥80-year-old adults. Another study[38] reported significant differences in adherence levels between age subgroups but did not confirm age as a significant predictor of medication nonadherence in multivariate analyses. Age was significantly associated with HL in one study[41] as patients with limited HL were significantly older compared to those with adequate HL. However, regression analyses did not confirm age as a predictor of limited HL (table 2).

Table 2. Results of age subgroup analyses on associations between age and health literacy, and age and medication adherence

Authors, year	Age subgroups reported	Age subgroup analyses
Lee *et al.*, 2013[35]	NA	None conducted
Lee *et al.*, 2017[36]	65-74 (57.0%) ≥75 (43.0%)	No significant differences in MA between age groups (χ^2=0.391, p=0.835)
Lu *et al.*, 2019[41]	≤60 (21.5%) 61-70 (43.0%) 71-80 (29.7%) >81 (5.7%)	Patients with limited HL were significantly older than those with adequate HL (p<0.05) Age was not a significant predictor for limited HL in ≥81-year-old patients compared to - patients ≤60 years old (AOR (95% CI) = 0.64 (0.24-1.72), p=0.380) - patients 61-70 years old (AOR (95% CI) = 1.19 (0.49-2.88), p=0.694) - patients 71-80 years old (AOR (95% CI) = 0.97 (0.40-2.40), p=0.955) Age was not a significant predictor for medication nonadherence in ≥81-year-old patients compared to - patients ≤60 years old (AOR (95% CI) = 0.67 (0.19-2.36), p=0.534) - patients 61-70 years old (AOR (95% CI) = 1.43 (0.49-4.17), p=0.518) - patients 71-80 years old (AOR (95% CI) = 1.02 (0.34-3.09), p=0.970)
Reading *et al.*, 2019[37]	<65 (27.2%) 65-74 (30.8%) 75-84 (30.5%) ≥85 (11.5%)	Nonadherence to medication significantly differed according to age (p<0.001) Age was a significant predictor for nonadherence to medication in <65-year-old patients compared to - patients 65-74 years old (AOR (95% CI) = 0.68 (0.55-0.83), p<0.001) - patients 75-84 years old (AOR (95% CI) = 0.67 (0.53-0.84), p<0.001) Age was not a significant predictor for nonadherence to medication in <65-year-old patients compared to - patients ≥85 years old (AOR (95% CI) = 0.86 (0.64-1.16), n.s.)
Saqlain *et*	65-75 (84.7%)	No significant differences in MA between age groups (χ^2=1.631, p=0.442)

al., 2019[44]	76-85 (11.1%) >85 (4.2%)	
Seong *et al*., 2019[38]	65-70 (32.1%) 70-79 (45.5%) ≥80 (22.4%)	Adherence to medication significantly differed with respect to age (χ^2=15.15, p<0.001) Age was a significant predictor for nonadherence to medication in ≥80-year-old patients (univariate regression) compared to - patients ≤79 years old (OR (95% CI) = 2.33 (1.291-4.207), p=0.005, univariate) Age was not a significant predictor for nonadherence to medication in ≥80-year-old patients (multivariate regression) compared to - patients ≤79 years old (OR (95% CI) = 1.24 (0.621-2.459), p=0.546, multivariate)
Shehadeh-Sheeny *et al*., 2013[45]	60-65 (21.5%) 66-75 (54.1%) 76-85 (24.4%)	No significant differences in MA between age groups (p=0.23)
Song & Park, 2020[39]	65-69 (38.8%) 70-79 (43.1%) ≥80 (18.1%)	Adherence to medication significantly differed with respect to age (Z=8.37, p<0.001). Post hoc analysis showed higher MA in 65-69-year-old adults (M=5.1 (2.3)) compared to 70-79 (M=4.0 (2.0)) and ≥80-year-old adults (M=3.0 (1.9)), respectively.
Wannasirikul *et al*., 2016[46]	60-65 (52.7%) 66-70 (47.3%)	None conducted

Notes: NA: Not available/ not reported.

Associations between health literacy and medication adherence

Results of the analyses on associations between HL and MA are depicted in table 3. In addition, an overview of cutoffs and categories used for the measures of HL and MA in the included studies are depicted in online supplementary table S3. All studies conducted analyses on these associations. Overall, six publications from five studies[35-37 39 44 46] reported positive and statistically significant associations between HL and MA while two studies[41 45] did not find any significant associations, and one study[38] reported mixed findings. In detail, one of two publications[35] from one study confirmed HL as the strongest predictor for MA in a hierarchical regression analysis while another publication[35] from this study found significantly positive associations between HL and MA but reported self-efficacy to be the strongest predictor for HL in their support vector machine (SVM) model. Another study[41] found no significant differences between limited compared to adequate HL in (medication) nonadherent patients with coronary heart disease. However, the study reported that patients with limited HL were more likely to be nonadherent to secondary adherence measures (i.e. heart-healthy lifestyle, alcohol intake control, exercise, stress management) and suggested that changing how to take your pills may be easier than changing lifestyle behaviour. In a study among ethnically diverse patients with atrial fibrillation[37], patients with inadequate levels of HL were significantly more likely to be nonadherent to medication than those with adequate levels of HL. In addition, the study found that included patients with self-reported physical inactivity (vs. physical activity), alcohol use (vs. no alcohol use), and diabetes mellitus were more likely to be nonadherent to medication, whereas patients with diagnosis of hypertension were less likely to be nonadherent to medication. A study on outpatients with hypertension[44] found positive and statistically

significant associations between HL and MA as well as a higher likelihood of patients with adequate levels of HL to be adherent to medication compared to patients with inadequate levels of HL. In their multivariate logistic regression, the same study found that in addition to adequate HL, self-reported good and moderate subjective health as well as independence in activities of daily living were also independent predictors of MA in the elderly. Another study[38] reported significant differences in adherence to antithrombotic medication by levels of HL but did not confirm HL as a significant predictor for MA in older adults. They concluded that a significant association between HL and MA might exist still since in their univariate regression the rate of inadequate HL was higher in the group of nonadherent patients compared to adherent patients. However, in their multivariate logistic regression, the authors[38] found only cognitive impairment to be a significant predictor of medication nonadherence in older patients with atrial fibrillation. One study[45] found no significant association between HL and MA in a population of female osteoporosis patients and found only self-reported income to be a significant predictor of adherence in the conducted multivariate logistic regression. Another study[39] found significantly positive associations between HL and MA. In their multiple regression analysis, the authors also found that income, number of chronic diseases, vision problems, and HL were significant predictors of MA. One other study[46] analysed the relationship between HL, MA, and blood pressure levels in primary care patients with hypertension using a Structural Equation Modeling (SEM) approach, which supported the existence of a causal relationship between these factors. Accordingly, HL had a positive but small statistically significant direct effect on MA. Literacy and cognitive ability had the biggest direct effects on both HL and MA. Additionally, HL had the biggest significantly negative direct effect on blood pressure levels (i.e. the higher the HL, the lower the blood pressure level). Based on the SEM, the authors of this study[46] suggested a mediator effect of HL on MA, even though no analysis was conducted. None of the other studies performed mediator and/or moderator analyses concerning HL and/or MA and other factors

312

Table 3. Detailed analyses of health literacy and medication adherence

Authors, year	Sample and setting	HL measures	MA measure	Key results	Associations between HL and MA and further outcomes
Lee *et al.*, 2013[35]	n=293, 65+ years M=74.4 years (6.3) Patients with chronic diseases from tertiary care hospitals in Cheonan, South Korea	BHLS 3 questions	MMAS-4	Mean HL was 8.3 (1.9) n=120 (41.0%) patients were adherent to medication	Significant associations between HL and MA (p=NA) Self-efficacy was strongest predictor for MA in SVM model Other factors significantly associated with MA were number of medication types, daily pill counts, duration after diagnosis
Lee *et al.*, 2017[36]	n=291, 65+ years M=NA Patients with chronic diseases from tertiary care hospital in South Korea	BHLS 15 questions	MMAS-8	Mean HL was 46.61 (12.66) n=89 (30.6%) patients were highly adherent with MMAS-Score of 8 Mean MA was at a medium level (M=6.32 (1.61))	HL positively correlated with MA (r=0.25, p<0.001) HL was strongest predictor of MA in hierarchical linear regression (β=0.190, p<0.001) Other significant predictors of MA in regression were perceived health status (β=0.132, p<0.02), use of magnifying glass (β=0.166, p<0.003), assistance with medication administration (β=0.120, p<0.035)
Lu *et al.*, 2019[41]	n=598 M=65.8 years (9.4) Patients with coronary heart disease from tertiary hospital in Shanghai, China	HLS-EU-Q16	MOS-SAS	HL was limited for n=444 (74.5%) and adequate for n=152 (25.5%) patients Patients with limited HL were significantly older than those with adequate HL (p=0.003) n=505 (84.7%) patients were adherent to medication	No significant associations between HL and MA (χ^2=NA, p=0.125) No significant predictive relationship between limited HL and medication nonadherence (AOR (95% CI) = 0.66 (0.39-1.11), p=0.113) Patients with limited HL compared to those with adequate HL were more likely to be nonadherent to overall heart-healthy lifestyle behaviour (AOR (95% CI) = 1.69 (1.13-2.53), p=0.010), exercise (AOR (95% CI) = 1.50 (1.01-2.22), p=0.046), alcohol intake control (AOR (95% CI) = 2.19 (1.21- 3.96), p=0.010), and stress management (AOR (95% CI) = 2.09 (1.32-3.29), p=0.002)
Reading *et al.*, 2019[37]	n=12159, 21+ years Age median was 72.7 and 70.1 years for adherent and nonadherent patients, respectively Ethnically diverse patients with atrial fibrillation from Northern California, USA	BHLS 3 questions	CARDIA (3 questions)	n=9349 (76,9%) patients had adequate HL n=771 (6.3%) patients were nonadherent to medication Significant differences in MA between age subgroups (p<0.001)	Patients with inadequate HL were more likely to be nonadherent to medication compared to those with adequate HL (AOR (95% CI) = 1.32 (1.09-1.60), p<0.01) in multivariate logistic regression model Patients were more likely to be nonadherent to medication if physically inactive (AOR (95% CI) = 1.57 (1.16-2.13), p<0.01), drinking alcohol (AOR (95% CI) = 1.91 (1.51-2.43), p<0.001), having diagnosis of diabetes mellitus (AOR (95% CI) = 1.22 (1.01-1.48), p<0.05), having 1-7 days of self-reported poor physical health (AOR (95% CI) = 1.43 (1.17-1.75), p<0.001) Patients were less likely to be nonadherent to medication if having diagnosis of hypertension (AOR (95% CI) = 0.72 (0.60-0.87), p<0.05), age between 65-74 (AOR (95% CI) = 0.68 (0.55-0.83), p<0.001) and age between 75-84 (AOR (95% CI) = 0.67 (0.53-0.84), p<0.001)

Saqlain *et al*., 2019[44]	n=262, 65+ years M=NA Outpatients with hypertension from tertiary health care centres in Islamabad, Pakistan	SILS	MMAS-4	n=98 (37.4%) patients had adequate HL n=102 (38.9%) patients were adherent to medication	Positive and statistically significant associations between HL and MA (χ^2=24.356, p<0.001) Patients with adequate HL were more likely to be adherent to medication compared to those with inadequate HL (OR (95% CI) = 3.37 (1.91-5.96), p<0.001) Other significant predictors of MA were self-reported good (OR (95% CI) = 4.25 (1.45-12.44), p<0.008) and moderate (OR (95% CI) = 3.54 (1.37-9.16), p<0.009) subjective health and independence in activities of daily living (OR (95% CI) = 2.97 (1.15-5.85), p<0.002)
Seong *et al*., 2019[38]	n=277, 65+ years M=74.2 (7.2) Outpatients with atrial fibrillation undergoing antithrombotic therapy in tertiary general hospital in South Korea	BHLS 3 questions	Single item	HL levels (M=7.9 (3.5)) were inadequate, marginal, and adequate for 28.1%, 45.5%, and 26.4% of patients, respectively n=139 (50.2%) patients were nonadherent to medication Significant differences in MA between age subgroups (p<0.001)	Positive and statistically significant associations between HL and MA (χ^2=22.00, p<0.001) Significant predictive relationship between marginal/ inadequate HL and medication nonadherence in univariate logistic regression analysis (OR (95% CI) = 2.55 (1.29-3.90), p=0.004) but not in multivariate logistic regression analysis (OR (95% CI) = 1.45 (0.79-2.64), p=0.232), where only cognitive impairment was significant predictor for medication nonadherence (OR (95% CI) = 2.63 (1.42-4.85), p=0.002)
Shehadeh-Sheeny *et al*., 2013[45]	n=303, 60+ years M= 71 (6.04) Female Arab patients with osteoporosis from three clinics in Israel	FCCHL	MPR	n=75 (24.8%) patients had high HL compared to n=164 (54.1%) and n=64 (21.1%) with medium and low HL, respectively n=125 (41.3%) patients had high MA	No significant associations between MA and HL (p=0.44) 46.7% of patients with high HL were more adherent to medication compared to 35.9% of patients with low HL In multivariate logistic regression only self-reported income was a significant predictor of MA (OR (95% CI) = 1.26 (1.01-1.58), p=0.037)
Song & Park, 2020[39]	n=116, 65+ years M=72.7 (6.1) Community-dwelling older adults in health care centre, South Korea	BHLS 15 questions	MMAS-8	Mean HL was 42.4 (6.6) Mean MA was at a medium level (M=4.3 (2.2))	HL positively correlated with MA (r=0.42, p<0.001) In multiple regression analysis HL was significant predictor of MA (β=0.23, p<0.001) Other significant predictors of MA were income (β=0.35, p<0.001), number of chronic diseases (β=-0.33, p<0.001), and vision problems (β=-0.32, p<0.001)

Wannasirikul *et al.*, 2016[46]	n=600, 60-70 years M=65.3 Patients with hypertension from primary health care centre in Sa Kaeo Province, Thailand	FCCHL	ARMS	Mean HL was 40.0 (10.4) HL levels were inadequate, marginal, and adequate for 48.7%, 43.8%, and 7.5% of patients, respectively MA was good for 98.3% of patients	SEM supports causal relationship between HL, MA, and blood pressure HL had a significantly positive direct effect on MA in SEM (β=0.08, p<0.05) Cognitive ability ((β=0.22, p<0.05) and literacy (β=0.46, p<0.05) had biggest and significantly positive direct effect on MA Literacy (β=0.15, p<0.05) and cognitive ability (β=0.52, p<0.05) had biggest and significantly positive direct effect on HL HL had biggest significantly negative direct effect on blood pressure level (β=-0.14, p<0.05) MA had a significantly negative direct effect on blood pressure level (β=--0.02, p<0.05) Results suggest mediator effect of HL on MA

Abbreviations: BHLS: Brief Health Literacy Screen, MMAS: Morisky Medication Adherence Scale, HLS-EU-Q: European HL Survey Questionnaire, MOS-SAS: Medical Outcomes Study Specific Adherence Scale, CARDIA: Coronary Artery Risk Development in Young Adults, SILS: Single Item Literacy Screener, FCCHL: Functional, Communicative, and Critical Health Literacy Questionnaire, MPR: Medication Possession Ratio, ARMS: Adherence to Refills and Medications Scale, NA: Not available/ not reported.

DISCUSSION

The aim of this study was to give a systematic overview of the associations between HL and MA in older adults. Although research on HL and MA in older adults has rapidly increased in the last years, mixed results are a common denominator in this area[15 52]. Accordingly, previous systematic reviews resulted in a range of conclusions as they included a variety of HL concepts, different (younger) age groups, and a range of methodologically different instruments (self-reports as well as performance-based measures) to assess HL[12 16 24 26 52]. To our knowledge, this is the first systematic review to focus specifically on self-reported HL while explicitly including studies with samples of older adults. We found that only few validated instruments of self-reported HL are used and that most studies still rely on legacy measures to assess HL even though their use has been criticized repeatedly and self-reports of HL offer a range of advantages[29]. Studies included in our review mostly assessed MA in older adults through self-reports, even though a wide range of tools is known[53 54].

Based on a rather high level of uncertainty due to low study quality and risk of bias, results in this review appear to be more consistent in contrast to previous reviews[15 16] as many included studies reported positive and statistically significant associations between HL and MA. This could be explained by the fact that only older adults (at least 66% of older adults in samples, not based on the samples´ mean age) were examined in the included studies and associations in this group may be more prominent compared to studies that also include subgroups of younger people. One review[24] for example aimed to review literature that examined HL and MA in older adults with cardiovascular disease or diabetes. Included studies in the review had to assess HL with legacy instruments only and had to include samples of participants with a "[…] mean age [of] at least 50 years or with at least a third of participants aged 50 years or older […]" and could not confirm an association between HL and MA. As stated earlier, inclusion of younger participants may have resulted in unknown bias from age. Yet another bias may have resulted from the utilization of legacy measures with different conceptualizations of HL since the REALM and TOFHLA, two of the most prominent legacy tools of HL, are confirmed to assess different aspects of literacy rather than HL and may thus be differently impacted by a person´s intelligence[29]. Accordingly, Loke *et al*. stated in their review that functional measures of HL may not be adequate and "[n]ew methods of measuring health literacy beyond the functional level are needed […]".

In another review, Ostini *et al*.[16] included studies with samples of all age groups, not disclosing how HL and MA were measured in these studies, and suggested the existence of a U-shaped relationship between HL and nonadherence as patients with high levels of HL may intentionally not adhere while those with low HL levels may unintentionally not adhere. Looking at the included studies in their review, only one study used a self-report measure of HL (BHLS) while all other used one of the performance-based legacy instruments. Since legacy measures of HL rather focus on literacy skills and we could not find any indication of a U-shaped relationship in our review, we want to point out that, while we cannot confirm or rule out a U-shaped relationship between literacy skills and MA, our review might suggest that it does not exist between self-reported HL and MA in older adults. While people with low literacy skills may not be able to understand/read labels/instructions and therefore not adhere (or rather unintentionally not comply) to their medication more often, people with higher literacy skills might read instructions first and subsequently (intentionally) decide not to take their medications due to e.g. possible side effects they read about. However, this phenomenon is not easily transferrable onto other and in some cases broader theoretical concepts of self-reported HL measures (e.g. HLS-EU-Q) since those not only include literacy skills but also other individual skills and situational aspects and may thus show another linear or non-linear

association with adherence. Since empirical data on possible associations between literacy and self-reported HL are still widely lacking, we need more research to explore and develop comprehensive theories in this area.

Six studies[37 38 41 44-46] included in this review found that a majority of participants in the respective samples reported limited (i.e. inadequate, low, marginal) HL. This is consistent with other research that showed that older people commonly reach only low levels of self-reported health literacy[3 25 32] even though this research is very scarce. HL was measured by versions of four different self-reports (BHLS[40 55], HLS-EU-Q[3], SILS[42], FCCHL[43]). This shows that self-reporting HL measures are still rarely utilized when examining older adults, even though the Health literacy Tool Shed[56] lists 29 self-report instruments for HL in English alone (58 without language restrictions).

MA was assessed through self-reports in all but one of the included studies[35-39 41 44 46]. Nevertheless, we recommend a more detailed description of operationalization of MA as many studies still use the concepts of adherence and compliance interchangeably. Interestingly, we had to exclude many studies from this review even though they assessed some form of adherence, because they only included measures of general preventive behaviour (e.g. physical activity) and not MA. However, the use of such secondary adherence measures might be a promising approach to get a more comprehensive picture of adherence in older adults[54]. Especially a multi-method approach could be helpful since self-reported adherence may also be affected by cognitive bias and/or social desirability in older adults. As such, the utilization of both direct (e.g. laboratory measures) and indirect (e.g. self-reports) measures of adherence[54 57] may help to get a better understanding of adherence and its associations with self-reported HL in older adults. A number of studies in this review also included measures of secondary prevention (e.g. physical activity, heart-healthy lifestyle behavior) as well as other factors (e.g. income, cognitive ability) providing further knowledge on possible confounders in the mechanisms between HL and MA. Accordingly, several studies confirmed multiple other factors as predictors for MA (e.g., health status[36 37 44], income[39 45], physical activity[37 44], cognitive ability[38 46]) and/ or HL (e.g., cognitive ability[46], stress management[41]). In a recent systematic review and meta-analysis by Lim et al.[58], the authors examined the associations between physical activity and HL and found that older adults with inadequate levels of HL were "[…] less likely […] to report engaging in physical activity […]" than those with adequate HL, showing the importance of also addressing secondary adherence measures in future research in this area. Notably, their review also included younger adults (samples with mean age ≥55 years) and different of HL measures (legacy measures and self-reports).

Even though we also encourage researchers to assess HL with a multi-method approach (e.g. subjective and objective instruments), we suggest a more rigorous differentiation in analysis and interpretation when comparing HL measures that are based on different concepts (e.g. legacy tools and self-reports). This may also help to clarify further the associations between self-reported HL and literacy as measured by legacy instruments. As stated by Nguyen *et al*.[29], a separation in analyses of objective and subjective measures of HL as well as a closer alignment of HL theory and measurement could help clarify the relationship between HL and MA. This idea was also supported by one of the studies[39] included in this review, which aimed at comparing two different measures of HL (self-report vs. legacy measure). The authors found that even though both measures were significantly and positively correlated to MA, only the self-report was a significant predictor for MA in older adults suggesting that self-reports may be more fitting to access HL when predicting MA since "[…] assessing older adults´ experiences of limited health literacy is more appropriate for catching any decreased medication adherence […]".

This review additionally confirms that age subgroup analyses are conducted very rarely for self-reported HL but quite often for MA. This may result from the fact that research on MA in the elderly is traditionally older than research on HL in the elderly and with regard to HL most studies still treat older people as a homogenous group[25]. Most studies in this review did not find any significant associations between age and MA and only two studies[37 39] reported significant differences in MA between age subgroups. Accordingly, one study[37] reported that young/ young-old people (21-65 years old) were more likely not to adhere to their medication compared to old/older adults (65-84 years old) but not oldest adults (≥85 years old). A second study[39] reported higher MA in 65-69-year-old adults compared to older/oldest adults (70-90 years old). Not surprisingly, only one study conducted analyses on the relationship between age and HL[41], showing that patients with limited HL were significantly older compared to those with adequate HL. Even though generalizability is very limited, these results reveal the necessity for more differentiated analyses (e.g. of subgroups) in future HL and MA research on older adults. In context of demographic change and increasing life expectancy, more differentiated analyses could help to understand specific needs and barriers of elderly (patient) populations with different chronic diseases. Importantly, definitions of *old age* are often inconsistent and include people from ages 60, 65, or 70 years and over. These dissimilarities in the definitions of old age may result from differences in cultural and/or economic standards (e.g. USA vs. Asia) and often manifest in different demographic changes and/or different life expectancies thus resulting in a different quality of health care in groups of older adults. Consequently, when looking at older adults´ health care and health outcomes, it is critical to include contextual aspects such as cultural or economic standards.

Studies in this review show some inconsistencies in the use of cutoffs, use, and wording of HL levels. Of all included studies, six studies[37 38 41 44-46] reported categories of HL (e.g. adequate) of which only three[38 41 44] reported cutoffs for these categories. Three publications[35 36 39] from two studies reported neither categories nor cutoffs for HL and only five publications[35 36 38 39 46] from four studies reported mean values of HL. For example, Shehadeh-Sheeny et al. calculated scores for low, medium, and high levels of HL while Wannasirikul et al. calculated scores for adequate, marginal, and inadequate HL levels even though no cutoffs were reported/available by neither the authors nor the FCCHL measure both studies used. The inconsistent use of cutoffs and wording may indicate a lack of certainty and experience in the application of self-reports enhancing the call for more differentiated research and the development of easy-to-use but still valid tools.

Strength and limitations

The strengths of this study include the exhaustive methodology and comprehensive search strategy that were used. As we followed a strict screening procedure, we are confident that we found all eligible studies. Since we excluded all studies that measured HL with performance-based instruments, we aimed to reduce bias resulting from fundamental differences in constructs and concepts. Although we see this exclusion as a considerable advantage, we cannot eliminate the possibility of bias still resulting from theoretical or practical differences in self-reports as some of them are built on more complex conceptual frameworks than others. Additionally, there are advantages in assessing HL in older adults with self-reports since they reduce the possible bias of performance-based measures resulting from fear of stigma and/or (time)

pressure. Nevertheless, we recognize the inherent limitations of self-reporting tools that may also have biased our results.

Other limitations should be considered. All studies included in this review were cross-sectional, thus we cannot determine any direction of causality. The fair to poor methodological quality of the included studies may also increase the risk of (unknown) bias. Given the heterogeneity of the studies, a meta-analysis (e.g. pooled odds ratios) could not be conducted, thus limiting further understanding of the relationship between HL and MA in older adults. Accordingly, certainty of evidence of these results is low. Additionally, our search strategy in this review limited included studies to English and German, which could bias results due to missing research in other languages. Finally, we were not able to include EMBASE as a database in our search. Even though, we are very confident that we did not miss a substantial amount of literature, this must be considered as a limitation of this review.

CONCLUSIONS

Based on a rather high level of uncertainty, included literature in this review suggests that self-reported HL and MA in older adults show a somewhat straightforward positive association. While previous research on HL and MA in older adults did not always find clear associations, many studies included in this review reported significantly positive associations between HL and MA. In addition, HL plays an important role as a predictor of MA in older adults as several studies in this review could confirm. However, other factors (e.g. cognitive ability) appear equally important in predicting MA in older adults, and future studies should also focus on secondary adherence measures (e.g. physical activity) when examining the associations between HL and MA in the elderly. Finally, study heterogeneity and methodological weaknesses reveal a definitive need for more differentiated research regarding different definitions, concepts, and measures of HL and MA as well as longitudinal research designs and studies that analyse age subgroups in older adults.

Acknowledgements

We would like to thank Dr. rer. biol. hum. Laura Inhestern for her advice during the preparation of the search for this review.

Author Contributions

All authors were involved in the design and planning of the review. MSS prepared, performed, and redefined the searches after consultation with SPH and CB. MSS and SPH performed screening and data extraction with the help of CB in case of disagreements or discussion. All authors contributed to the data analysis and interpretation. MSS wrote the first draft which was critically revised by SPH and CB.

Ethics Approval Statement

This study does not involve human participants, as it is a systematic review.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Patient consent

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information.

REFERENCES

1 United Nations, Department of Economic and Social Affairs, Population Division. World Population Ageing 2019: Highlights (ST/ESA/SER.A/430). 2019.

2 Ratzan SC, Parker RM. Health literacy - identification and response. *J Health Commun* 2006;**11**:713-5.doi:10.1080/10810730601031090

3 Consortium H-E. Comparative Report on Health Literacy in Eight EU Member States. The European Health Literacy Project 2009–2012. Vienna: Ludwig Boltzmann Institute for Health Promotion Research 2012.

4 Berkman ND, Sheridan SL, Donahue KE, et al. Low health literacy and health outcomes: an updated systematic review. *Ann Intern Med* 2011;**155**:97-107.doi:10.7326/0003-4819-155-2-201107190-00005

5 Chesser AK, Keene Woods N, Smothers K, et al. Health Literacy and Older Adults: A Systematic Review. *Gerontol Geriatr Med* 2016;**2**:2333721416630492.doi:10.1177/2333721416630492

6 Vogt D, Schaeffer D, Messer M, et al. Health literacy in old age: results of a German cross-sectional study. *Health Promot Int* 2018;**33**:739-47.doi:10.1093/heapro/dax012

7 Wolf MS, Feinglass J, Thompson J, et al. In search of 'low health literacy': threshold vs. gradient effect of literacy on health status and mortality. *Soc Sci Med* 2010;**70**:1335-41.doi:10.1016/j.socscimed.2009.12.013

8 Gast A, Mathes T. Medication adherence influencing factors—an (updated) overview of systematic reviews. *Systematic Reviews* 2019;**8**:1-17.doi:10.1186/s13643-019-1014-8

9 Hoel RW, Giddings Connolly RM, Takahashi PY. Polypharmacy Management in Older Patients. *Mayo Clinic Proceedings* 2021;**96**:242-56.doi:10.1016/j.mayocp.2020.06.012

10 Chiatti C, Bustacchini S, Furneri G, et al. The economic burden of inappropriate drug prescribing, lack of adherence and compliance, adverse drug events in older people: a systematic review. *Drug Saf* 2012;**35 Suppl 1**:73-87.doi:10.1007/BF03319105

11 Huang YM, Shiyanbola OO, Smith PD. Association of health literacy and medication self-efficacy with medication adherence and diabetes control. *Patient Prefer Adherence* 2018;**12**:793-802.doi:10.2147/PPA.S153312

12 Martins NFF, Abreu DPG, Silva BTD, et al. Functional health literacy and adherence to the medication in older adults: integrative review. *Rev Bras Enferm* 2017;**70**:868-74.doi:10.1590/0034-7167-2016-0625

13 Park NH, Song MS, Shin SY, et al. The effects of medication adherence and health literacy on health-related quality of life in older people with hypertension. *Int J Older People Nurs* 2018;**13**:e12196.doi:10.1111/opn.12196

14 Roh YH, Koh YD, Noh JH, et al. Effect of health literacy on adherence to osteoporosis treatment among patients with distal radius fracture. *Arch Osteoporos* 2017;**12**:42.doi:10.1007/s11657-017-0337-0

15 Zhang NJ, Terry A, McHorney CA. Impact of health literacy on medication adherence: a systematic review and meta-analysis. *Ann Pharmacother* 2014;**48**:741-51.doi:10.1177/1060028014526562

16 Ostini R, Kairuz T. Investigating the association between health literacy and non-adherence. *International journal of clinical pharmacy* 2014;**36**:36-44.doi:10.1007/s11096-013-9895-4

17 Lindquist LA, Go L, Fleisher J, et al. Relationship of health literacy to intentional and unintentional non-adherence of hospital discharge medications. *J Gen Intern Med* 2012;**27**:173-8.doi:10.1007/s11606-011-1886-3

18 Wolf MS, Davis TC, Osborn CY, et al. Literacy, self-efficacy, and HIV medication adherence. *Patient Educ Couns* 2007;**65**:253-60.doi:10.1016/j.pec.2006.08.006

19 Kripalani S, Gatti ME, Jacobson TA. Association of age, health literacy, and medication management strategies with cardiovascular medication adherence. *Patient Educ Couns* 2010;**81**:177-81.doi:10.1016/j.pec.2010.04.030

20 Bauer AM, Schillinger D, Parker MM, et al. Health literacy and antidepressant medication adherence among adults with diabetes: the diabetes study of Northern California (DISTANCE). *J Gen Intern Med* 2013;**28**:1181-7.doi:10.1007/s11606-013-2402-8

21 Mayo-Gamble TL, Mouton C. Examining the Association Between Health Literacy and Medication Adherence Among Older Adults. *Health Commun* 2018;**33**:1124-30.doi:10.1080/10410236.2017.1331311
22 Mosher HJ, Lund BC, Kripalani S, et al. Association of health literacy with medication knowledge, adherence, and adverse drug events among elderly veterans. *J Health Commun* 2012;**17 Suppl 3**:241-51.doi:10.1080/10810730.2012.712611
23 Fang MC, Machtinger EL, Wang F, et al. Health literacy and anticoagulation-related outcomes among patients taking warfarin. *J Gen Intern Med* 2006;**21**:841-6.doi:10.1111/j.1525-1497.2006.00537.x
24 Loke YK, Hinz I, Wang X, et al. Systematic review of consistency between adherence to cardiovascular or diabetes medication and health literacy in older adults. *Ann Pharmacother* 2012;**46**:863-72.doi:10.1345/aph.1Q718
25 Vogt D, Berens EM, Schaeffer D. Gesundheitskompetenz im höheren Lebensalter [Health Literacy in Advanced Age]. *Gesundheitswesen* 2020;**82**:407-12.doi:10.1055/a-0667-8382
26 Geboers B, Brainard JS, Loke YK, et al. The association of health literacy with adherence in older adults, and its role in interventions: a systematic meta-review. *BMC Public Health* 2015;**15**:903.doi:10.1186/s12889-015-2251-y
27 Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened screening instrument. *Fam Med* 1993;**25**:391-5
28 Parker RM, Baker DW, Williams MV, et al. The test of functional health literacy in adults: a new instrument for measuring patients' literacy skills. *J Gen Intern Med* 1995;**10**:537-41.doi:10.1007/BF02640361
29 Nguyen TH, Paasche-Orlow MK, McCormack LA. The state of the science of health literacy measurement. *Information Services & Use* 2017;**37**:189-203.doi:10.3233/ISU-170827
30 Kobayashi LC, Wardle J, Wolf MS, et al. Aging and Functional Health Literacy: A Systematic Review and Meta-Analysis. *J Gerontol B Psychol Sci Soc Sci* 2016;**71**:445-57.doi:10.1093/geronb/gbu161
31 Sørensen K, Van den Broucke S, Pelikan JM, et al. Measuring health literacy in populations: illuminating the design and development process of the European Health Literacy Survey Questionnaire (HLS-EU-Q). *BMC Public Health* 2013;**13**:948.doi:10.1186/1471-2458-13-948
32 Berens EM, Vogt D, Messer M, et al. Health literacy among different age groups in Germany: results of a cross-sectional survey. *BMC Public Health* 2016;**16**:1151.doi:10.1186/s12889-016-3810-6
33 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.doi:10.1371/journal.pmed.1000097
34 National Heart, Lung, and Blood Institute.. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, 2014. Available: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort [Accessed 05 May 2020].
35 Lee SK, Kang BY, Kim HG, et al. Predictors of medication adherence in elderly patients with chronic diseases using support vector machine models. *Healthc Inform Res* 2013;**19**:33-41.doi:10.4258/hir.2013.19.1.33
36 Lee YM, Yu HY, You MA, et al. Impact of health literacy on medication adherence in older people with chronic diseases. *Collegian* 2017;**24**:11-8.doi:10.1016/j.colegn.2015.08.003
37 Reading SR, Black MH, Singer DE, et al. Risk factors for medication non-adherence among atrial fibrillation patients. *BMC Cardiovasc Disord* 2019;**19**:38.doi:10.1186/s12872-019-1019-1
38 Seong HJ, Lee K, Kim BH, et al. Cognitive Impairment Is Independently Associated with Non-Adherence to Antithrombotic Therapy in Older Patients with Atrial Fibrillation. *Int J Environ Res Public Health* 2019;**16**.doi:10.3390/ijerph16152698
39 Song MS, Park S. Comparing two health literacy measurements used for assessing older adults' medication adherence. *J Clin Nurs* 2020;**29**:4313-20.doi:10.1111/jocn.15468
40 Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. *Fam Med* 2004;**36**:588-94

41 Lu M, Ma J, Lin Y, et al. Relationship between patient's health literacy and adherence to coronary heart disease secondary prevention measures. *J Clin Nurs* 2019;**28**:2833-43.doi:10.1111/jocn.14865
42 Morris NS, MacLean CD, Chew LD, et al. The Single Item Literacy Screener: evaluation of a brief instrument to identify limited reading ability. *BMC Fam Pract* 2006;**7**:21.doi:10.1186/1471-2296-7-21
43 Ishikawa H, Takeuchi T, Yano E. Measuring functional, communicative, and critical health literacy among diabetic patients. *Diabetes Care* 2008;**31**:874-9.doi:10.2337/dc07-1932
44 Saqlain M, Riaz A, Malik MN, et al. Medication Adherence and Its Association with Health Literacy and Performance in Activities of Daily Livings among Elderly Hypertensive Patients in Islamabad, Pakistan. *Medicina (Kaunas)* 2019;**55**.doi:10.3390/medicina55050163
45 Shehadeh-Sheeny A, Eilat-Tsanani S, Bishara E, et al. Knowledge and health literacy are not associated with osteoporotic medication adherence, however income is, in Arab postmenopausal women. *Patient Educ Couns* 2013;**93**:282-8.doi:10.1016/j.pec.2013.06.014
46 Wannasirikul P, Termsirikulchai L, Sujirarat D, et al. Health Literacy, Medication Adherence, and Blood Pressure Level among Hypertensive Older Adults Treated at Primary Health Care Centers. *Southeast Asian J Trop Med Public Health* 2016;**47**:109-20
47 Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;**24**:67-74.doi:10.1097/00005650-198601000-00007
48 Sherbourne CD, Hays RD, Ordway L, et al. Antecedents of adherence to medical recommendations: results from the Medical Outcomes Study. *J Behav Med* 1992;**15**:447-68.doi:10.1007/BF00844941
49 Wu JR, DeWalt DA, Baker DW, et al. A single-item self-report medication adherence question predicts hospitalisation and death in patients with heart failure. *J Clin Nurs* 2014;**23**:2554-64.doi:10.1111/jocn.12471
50 Cutter GR, Burke GL, Dyer AR, et al. Cardiovascular risk factors in young adults. The CARDIA baseline monograph. *Control Clin Trials* 1991;**12**:1S-77S.doi:10.1016/0197-2456(91)90002-4
51 Kripalani S, Risser J, Gatti ME, et al. Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients with chronic disease. *Value Health* 2009;**12**:118-23.doi:10.1111/j.1524-4733.2008.00400.x
52 Miller TA. Health literacy and adherence to medical treatment in chronic and acute illness: A meta-analysis. *Patient Educ Couns* 2016;**99**:1079-86.doi:10.1016/j.pec.2016.01.020
53 Lam WY, Fresco P. Medication Adherence Measures: An Overview. *Biomed Res Int* 2015;**2015**:217047.doi:10.1155/2015/217047
54 Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment adherence. *Med Pharm Rep* 2019;**92**:117-22.doi:10.15386/mpr-1201
55 Chew LD, Griffin JM, Partin MR, et al. Validation of screening questions for limited health literacy in a large VA outpatient population. *J Gen Intern Med* 2008;**23**:561-6.doi:10.1007/s11606-008-0520-5
56 Health Literacy Tool Shed, 2020. Available: https://healthliteracy.bu.edu. [Accessed 17 August 2020].
57 McRae-Clark AL, Baker NL, Sonne SC, et al. Concordance of Direct and Indirect Measures of Medication Adherence in A Treatment Trial for Cannabis Dependence. *J Subst Abuse Treat* 2015;**57**:70-4.doi:10.1016/j.jsat.2015.05.002
58 Lim ML, van Schooten KS, Radford KA, et al. Association between health literacy and physical activity in older people: a systematic review and meta-analysis. *Health Promot Int* 2020;**daaa072.**doi:10.1093/heapro/daaa072

Figure 1. PRISMA Flow Diagram
Notes: *no HL measure available (n=184), NVS (n=35), REALM (n=63), TOFHLA (n=90), other performance-based measure (n=5)
**only for samples that not exclusively focus on elders

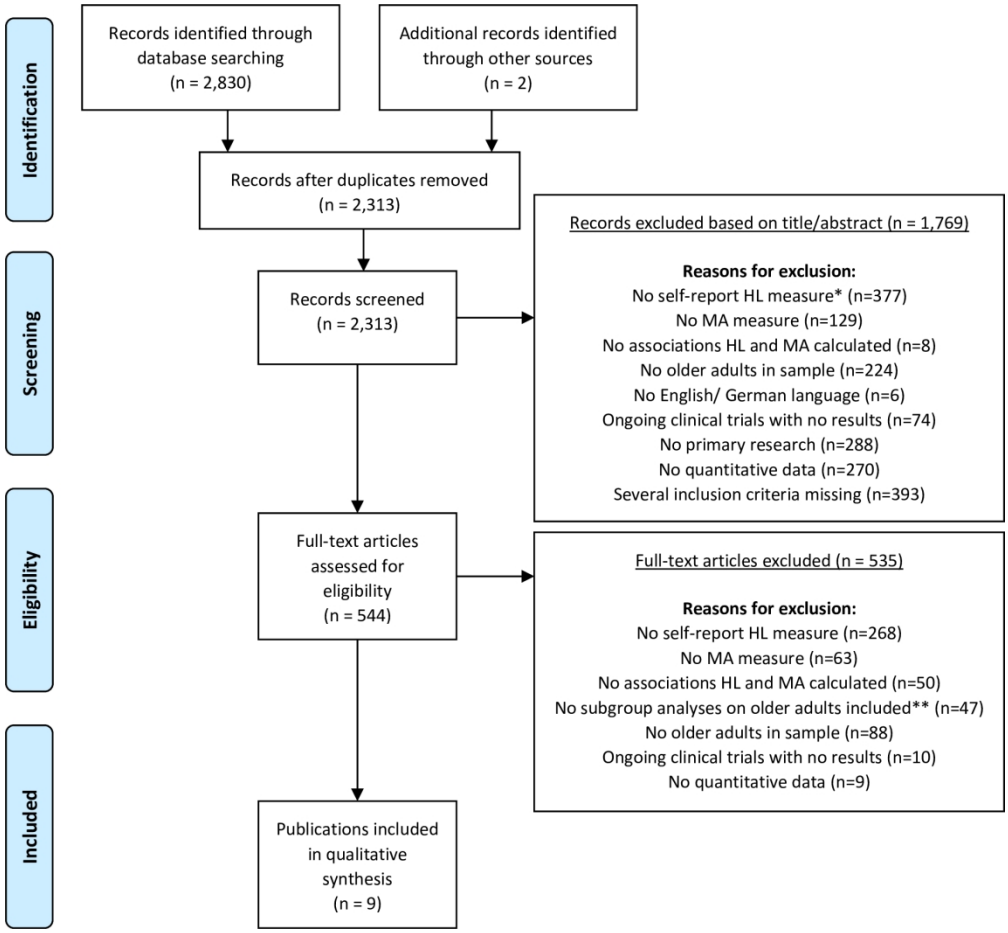

Figure 1. PRISMA Flow Diagram
Notes: *no HL measure available (n=184), NVS (n=35), REALM (n=63), TOFHLA (n=90), other performance-based measure (n=5)
**only for samples that not exclusively focus on elders

168x155mm (300 x 300 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4, Table S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 4-5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 4-5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5 Due to study heterogeneity, a narrative synthesis was applied.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 5-6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Pages 6-14, Tables 1-3 & S3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 6, Table S2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 6-14, Tables 1-3 & S3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 6-7, Tables 1 and S2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 5-6, and 17-18
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 6, 16, and 19 Table S2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 15-17
	23b	Discuss any limitations of the evidence included in the review.	Pages 17-18
	23c	Discuss any limitations of the review processes used.	Pages 17-18
	23d	Discuss implications of the results for practice, policy, and future research.	Page 18
OTHER INFORMATION			

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4, File S2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	File S2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 19
Competing interests	26	Declare any competing interests of review authors.	Page 19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Template data collection forms on reasonable request, Pages 4-6, tables 1-3 & S3

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Citation

Moritz Schoenfeld, Stefanie Pfisterer-Heise, Corinna Bergelt. Self-reported health literacy and treatment adherence in older adults: a systematic review. PROSPERO 2019 CRD42019141028 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019141028

Review question

The overall objective of this study is to systematically review all published evidence on the levels and associations of self-reported health literacy and treatment adherence in older adults (over 60 years old).

It specifically aims to:

1. Examine the levels of self-reported health literacy and treatment adherence in (if available, different subgroups of) older adults

2. Evaluate the associations of self-reported health literacy and treatment adherence in older adults

3. Identify how self-reported health literacy and treatment adherence in older adults are measured

4. Investigate moderator and mediator effects of other psychosocial and sociodemographic factors (may include: Quality of life, socioeconomic status, illness perception, physical activity, age, sex)

Searches

A research librarian was consulted for advice on databases prior to the literature search.

The following five electronic databases will be searched:

PubMed, CINAHL, Cochrane Library, Epistemonikos, LIVIVO.

All databases will be searched (adapted searches) from July, 15, 2019 to July 30, 2019. Search was updated in October 2020. Searches will be limited to human subjects.

All eligible literature published until July 2019 will be included (Updated search: October 2020, included as well). Articles must be written in English or German.

In addition, articles will be searched by hand for cross-references. References will be exported to Endnote and duplicates deleted.

Search terms:

"health literacy", "illiteracy", "treatment adherence and compliance", "patient compliance", "compliance", "patient adherence", "adherence", "non-adherence", "nonadherence", "medication adherence", "discontinuation", "non-compliance", "noncompliance", "termination", "refill", "aged", "old", "older", "elderly", geriatric", "oldest", "elders".

Keywords: "health literacy", "adherence", "patient adherence", "patient compliance", "compliance", "aged", "old", "older", "elderly".

Types of study to be included

Primary research (quantitative only, baseline data) will be included. Included study types will be: Randomized controlled trials, prospective and retrospective cohort studies, and cross-sectional studies. Articles must be written in English or German.

Only original, peer-reviewed studies will be included. No systematic reviews, commentaries, conference abstracts, books, meta-analyses or grey literature will be included.

Condition or domain being studied

Levels and associations of self-reported health literacy (subjective measures) and treatment adherence in older (60+ years) adults will be assessed as primary outcomes.

Other psychosocial and sociodemographic factors will be investigated for possible moderator or mediator effects. Currently, there are no reviews that specifically focus on the associations of self-reported (subjective) outcome measures of health literacy and treatment adherence in older adults.

Participants/population

Studies that examined older adults aged 60 years and older will be included. Only studies with at least 2/3 of older adults in samples will be included.

Intervention(s), exposure(s)

Included studies must contain at least one (validated) measure of self-reported health literacy and treatment adherence and must provide at least one measure (e.g. mean) to calculate associations (i.e. correlation, effect size) between health literacy and treatment adherence.

Only studies that assessed health literacy with self-report (subjective) measures will be included. Studies that assessed health literacy with performance-based (objective) tests/ measures will not be included.

Comparator(s)/control

Different baseline levels and associations of health literacy and treatment adherence will be analyzed.

Main outcome(s)

Health literacy (subjective measure only)

Treatment adherence (including medication adherence). Treatment adherence may include pill counts, self-reports, questionnaires, screeners, and refill records.

Measures of effect

Baseline.

Additional outcome(s)

None.

Measures of effect

Not applicable.

Data extraction (selection and coding)

All search results will be exported to Endnote X8 reference management software and screened for duplicates.

Titles and abstract will be screened by two reviewers independently using a standardized checklist that will be developed for this purpose. Both reviewers will then assess full-text articles for eligibility based on clearly stated criteria. Cases of missing consensus will be discussed and, if necessary, resolved by a third reviewer. Inclusion and exclusion of all studies will be documented and presented according to PRISMA guidelines.

A data extraction sheet for data extraction from eligible studies will be developed and pilot tested, and data will be documented in Microsoft Excel.

Data extraction will include the following criteria: Title, authors, year published, journal title, assessment of health literacy and treatment adherence, psychosocial and sociodemographic outcomes with moderator and mediator effects, statistical measures to calculate associations between health literacy and treatment adherence, population and setting details, sample size, age groups, statistical significance if available.

Risk of bias (quality) assessment

Quality assessment of included full-text studies will be conducted by both reviewers using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

The NIH was deemed appropriate, since only baseline data (levels and associations of health literacy and treatment adherence) will be analyzed.

Strategy for data synthesis

Data synthesis will be conducted in accordance to PRISMA guidelines (Liberati et al., 2009).

Since only studies with subjective measures of health literacy will be included, high heterogeneity (e.g. different measures of health literacy and treatment adherence) is expected. Accordingly, a narrative synthesis will be conducted to summarize the studies thematically.

Analysis of subgroups or subsets

If available, subgroup analyses of the levels and associations of health literacy and treatment adherence in different age groups (e.g. 60-64, 65-69, 70-74, 75-79, over 80) will be conducted.

Contact details for further information

Moritz Schoenfeld
mo.schoenfeld@uke.de

Organisational affiliation of the review

University Medical Center Hamburg-Eppendorf, Department of Medical Psychology

https://www.uke.de/kliniken-institute/institute/institut-und-poliklinik-f%C3%BCr-medizinische-psychologie/index.html

Review team members and their organisational affiliations

Mr Moritz Schoenfeld. University Medical Center Hamburg-Eppendorf, Department of Medical Psychology
Mrs Stefanie Pfisterer-Heise. University Medical Center Hamburg-Eppendorf, Department of Biochemistry and Molecular Cell Biology
Professor Corinna Bergelt. University Medical Center Hamburg-Eppendorf, Deparment of Medical Psychology

Type and method of review

Narrative synthesis, Systematic review

Anticipated or actual start date

01 May 2019

Anticipated completion date

30 September 2020

Funding sources/sponsors

None.

Conflicts of interest

Language

English

Country

Germany

Stage of review

Review Completed not published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Health Literacy; Humans; Medication Adherence; Self Report

Date of registration in PROSPERO

24 October 2019

Date of first submission

12 July 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Search was updated in October 2020 and slightly adapted to possibly include newer and relevant literature. Age inclusion criteria were slightly adapted to include studies with (at least 2/3 of) participants 60 years and older, since we noticed some dissimilarities in definitions of "old age" in the studies found in our preliminary search, and decided to also include those studies as they appeared relevant to our research question.The review is now being prepared for dissemination and publication.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

24 October 2019
13 October 2020
10 March 2021

Table S1. Search strategy used in different databases	
Source of search	Search terms
PubMed (MEDLINE)	(health literacy OR illiteracy) AND (treatment adherence and compliance OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR nonadherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR termination OR refill) AND (aged OR old OR older OR elderly OR geriatric OR oldest OR elders)
CINAHL	(health literacy OR illiteracy) AND (treatment adherence and compliance OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR nonadherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR termination OR refill) AND (aged OR old OR older OR elderly OR geriatric OR oldest OR elders)
COCHRANE	health literacy OR illiteracy in Title Abstract Keyword AND treatment adherence OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR nonadherence OR termination OR refill in Title Abstract Keyword AND aged OR old OR older OR elderly OR geriatric OR oldest OR elders in Title Abstract Keyword - (Word variations have been searched)
LIVIVO	("health literacy") AND ("patient compliance and compliance" OR "patient adherence" OR adherence) AND (aged OR old OR older OR elderly)
Epistemonikos	(advanced_title_en:(health literacy OR illiteracy) OR advanced_abstract_en:(health literacy OR illiteracy)) AND (advanced_title_en:(treatment adherence OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR nonadherence OR termination OR refill) OR advanced_abstract_en:(patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR nonadherence OR termination OR refill)) AND (advanced_title_en:(aged OR old OR older OR elderly OR geriatric OR oldest OR elders) OR advanced_abstract_en:(aged OR old OR older OR elderly OR geriatric OR oldest OR elders)) [Filters: protocol=no]

PubMed Search

Search: **(health literacy OR illiteracy) AND (treatment adherence and compliance OR patient compliance OR compliance OR patient adherence OR adherence OR non-adherence OR nonadherence OR medication adherence OR discontinuation OR non-compliance OR noncompliance OR termination OR refill) AND (aged OR old OR older OR elderly OR geriatric OR oldest OR elders)**

("health literacy"[MeSH Terms] OR ("health"[All Fields] AND "literacy"[All Fields]) OR "health literacy"[All Fields] OR ("literacy"[MeSH Terms] OR "literacy"[All Fields] OR "illiteracy"[All Fields])) AND ("treatment adherence and compliance"[MeSH Terms] OR ("treatment"[All Fields] AND "adherence"[All Fields] AND "compliance"[All Fields]) OR "treatment adherence and compliance"[All Fields] OR ("patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields]) OR ("compliances"[All Fields] OR "patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "compliance"[All Fields] OR "compliance"[MeSH Terms]) OR ("patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR ("patient"[All Fields] AND "adherence"[All Fields]) OR

"patient adherence"[All Fields]) OR ("adherance"[All Fields] OR "adhere"[All Fields] OR "adhered"[All Fields] OR "adherence"[All Fields] OR "adherences"[All Fields] OR "adherent"[All Fields] OR "adherents"[All Fields] OR "adherer"[All Fields] OR "adherers"[All Fields] OR "adheres"[All Fields] OR "adhering"[All Fields]) OR "non-adherence"[All Fields] OR ("nonadherence"[All Fields] OR "nonadherent"[All Fields] OR "nonadherents"[All Fields] OR "nonadherers"[All Fields]) OR ("medication adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "medication adherence"[All Fields]) OR ("discontinuance"[All Fields] OR "discontinuances"[All Fields] OR "discontinuated"[All Fields] OR "discontinuation"[All Fields] OR "discontinuations"[All Fields] OR "discontinue"[All Fields] OR "discontinued"[All Fields] OR "discontinuer"[All Fields] OR "discontinuers"[All Fields] OR "discontinues"[All Fields] OR "discontinuing"[All Fields]) OR "non-compliance"[All Fields] OR ("noncompliant"[All Fields] OR "noncompliants"[All Fields] OR "noncompliers"[All Fields] OR "noncomplying"[All Fields] OR "patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "noncompliance"[All Fields] OR "noncompliances"[All Fields]) OR ("terminal"[All Fields] OR "terminal s"[All Fields] OR "terminally"[All Fields] OR "terminals"[All Fields] OR "terminate"[All Fields] OR "terminated"[All Fields] OR "terminates"[All Fields] OR "terminating"[All Fields] OR "termination"[All Fields] OR "terminations"[All Fields] OR "terminator"[All Fields] OR "terminators"[All Fields]) OR ("refill"[All Fields] OR "refillable"[All Fields] OR "refilled"[All Fields] OR "refilling"[All Fields] OR "refills"[All Fields])) AND ("aged"[MeSH Terms] OR "aged"[All Fields] OR "old"[All Fields] OR ("older"[All Fields] OR "olders"[All Fields]) OR ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("geriatric"[All Fields] OR "geriatrics"[MeSH Terms] OR "geriatrics"[All Fields]) OR "oldest"[All Fields] OR ("elder s"[All Fields] OR "elders"[All Fields] OR "sambucus"[MeSH Terms] OR "sambucus"[All Fields] OR "elder"[All Fields]))

Table S2. Quality assessment of reviewed studies based on NHLBI

Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total[1]
Lee et al., 2013	+	+	NR	+	-	-	-	+	+	-	+	-	NA	+	fair
Lee et al., 2017	+	+	+	+	+	-	-	-	+	-	+	-	NA	+	fair
Lu et al., 2019	+	+	+	+	+	-	-	-	+	-	+	NR	NA	+	fair
Reading et al., 2019	+	+	+	+	-	-	-	+	-	-	-	NR	NA	+	poor
Saqlain et al., 2019	+	+	+	+	+	-	-	+	+	-	+	-	NA	+	fair
Seong et al., 2019	+	+	NR	+	+	-	-	+	+	-	+	NR	NA	+	fair
Shehadeh-Sheeny et al., 2013	+	+	+	+	-	-	-	+	+	-	+	-	NA	+	fair
Song & Park, 2020	+	+	+	+	+	-	-	-	+	-	+	NR	NA	+	fair
Wannasirikul et al., 2016	+	+	+	+	+	-	-	+	+	-	+	-	NA	+	fair

Notes and abbreviations: [1]Total scores were calculated based on the single scores and a critical appraisal of the methodological quality of each study in accordance with the NHLBI.

NR: Not relevant, NA/NR: Not available/not reported.

Criteria: 1. Was the research question or objective in this paper clearly stated?; 2. Was the study population clearly specified and defined?; 3. Was the participation rate of eligible persons at least 50%?; 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?; 5. Was a sample size justification, power description, or variance and effect estimates provided?; 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?; 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?; 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?; 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; 10. Was the exposure(s) assessed more than once over time?; 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; 12. Were the outcome assessors blinded to the exposure status of participants?; 13. Was loss to follow-up after baseline 20% or less?; 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?.

The NHLBI can be found in: National Heart, Lung, and Blood Institute. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. 2014. Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort.

Table S3. Cutoffs and categorization of measures of health literacy and medication adherence

Authors, year	HL measures	Reported range and cutoff/ categories of HL scores	MA measure	Reported range and cutoff/ categories of MA scores
Lee *et al.*, 2013	BHLS 3 questions	Range of overall HL scores: 3-15 with higher scores indicating higher HL Cutoff/ categories: NA	MMAS-4	Range of overall MA scores: 0-4 with higher scores indicating higher MA Cutoff/ categories: MA scores were dichotomized into nonadherence (scores ≤ 2) and adherence (scores ≥3)
Lee *et al.*, 2017	BHLS 15 questions	Range of overall HL scores: 15-75 with higher scores indicating higher HL Cutoff/ categories: NA	MMAS-8	Range of overall MA scores: 0-8 with higher scores indicating higher MA Cutoff/ categories: Scores were categorized into high (scores of 8), medium (scores 6-7), and low (scores ≤5) MA
Lu *et al.*, 2019	HLS-EU-Q16	Range of overall HL scores: 0-50 with higher scores indicating higher HL Cutoff/ categories: Scores ≤33 indicated limited HL, scores >34 indicated adequate HL	MOS-SAS	Range of MA scores: 0-5 with higher scores indicating higher MA Cutoff/ categories: Scores were dichotomized into adherence (scores ≥4) and nonadherence (scores ≥3)
Reading *et al.*, 2019	BHLS 3 questions	Range of overall HL scores: 3-15 with higher scores indicating higher HL Cutoff/ categories: HL was dichotomized into adequate and inadequate, but no cutoffs were reported	CARDIA (3 questions)	Range of MA scores: NA Cutoff/ categories: Nonadherence was defined according to scale for each answer (1. answers "75% of the time" or less; 2. /3. answers "once per week" or more)
Saqlain *et al.*, 2019	SILS	Range of overall HL scores: 1-5 with higher scores indicating lower HL Cutoff/ categories: HL scores ≥3 indicated inadequate HL and scores ≤2 indicated adequate HL	MMAS-4	Range of overall MA scores: 0-4 with higher scores indicating higher MA Cutoff/ categories: MA scores were dichotomized into nonadherence (scores ≤ 3) and adherence (scores of 4)
Seong *et al.*, 2019	BHLS 3 questions	Range of overall HL scores: 0-12 with higher scores indicating higher HL Cutoff/ categories: HL scores were categorized into inadequate (scores ≤6), marginal (scores 7-10), and adequate (scores 11-12) HL	Single item ("In the past week, have you forgotten to take your antithrombotic medication for various reasons?")	Range of overall MA scores: 1-5 with higher scores indicating higher MA Cutoff/ categories: MA scores were dichotomized into nonadherence (scores ≤ 5) and adherence (scores of 6)
Shehadeh-Sheeny *et al.*, 2013	FCCHL	Range of overall HL scores: NA, higher scores indicating higher HL Cutoff/ categories: HL scores were categorized into low, medium, and high HL, but no cut offs were reported/ are available	MPR	Range of overall MA scores: 0-1 (0%-100%), higher scores indicating higher MA Cutoff/ categories: MA scores were categorized into low (MPR ≤ 0.2) and high (MPR ≥ 0.8) MA

Song & Park, 2020	BHLS 15 questions	Range of overall HL scores: 15-75 with higher scores indicating higher HL Cutoff/ categories: NA	MMAS-8	Range of overall MA scores: 0-8 with higher scores indicating higher MA Cutoff/ categories: NA
Wannasirikul *et al*., 2016	FCCHL	Range of overall HL scores: 17-68 with higher scores indicating higher HL Cutoff/ categories: HL scores were categorized into inadequate, marginal, and adequate HL, but no cut offs were reported/ are available	ARMS	Range of overall MA scores: 14-56 with higher scores indicating higher MA Cutoff/ categories: NA

Abbreviations: HL: Health literacy, MA: Medication Adherence, BHLS: Brief Health Literacy Screen, MMAS: Morisky Medication Adherence Scale, HLS-EU-Q: European Health Literacy Survey Questionnaire, MOS-SAS: Medical Outcomes Study Specific Adherence Scale, CARDIA: Coronary Artery Risk Development in Young Adults, SILS: Single Item Literacy Screener, FCCHL: Functional, Communicative, and Critical Health Literacy Questionnaire, MPR: Medication Possession Ratio, ARMS: Adherence to Refills and Medications Scale, NA: Not available/ not reported.