

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3 **1 Self-reported health literacy and medication adherence in older adults: A systematic review**

4 2 Schönfeld MS¹, Pfisterer-Heise S², Bergelt C^{1,3}

5
6 3

7
8 ¹Department of Medical Psychology, University Medical Center Hamburg-Eppendorf, Hamburg,
9 Germany

10 ²Department of Biochemistry and Molecular Cell Biology, University Medical Center Hamburg-
11 Eppendorf, Hamburg, Germany

12 ³Department of Medical Psychology, University Medicine Greifswald, Greifswald, Germany
13

14
15 **Corresponding author:**

16 **Moritz Sebastian Schönfeld**

17 University Medical Center Hamburg-Eppendorf

18 Department of Medical Psychology

19 Martinstraße 52

20 20246 Hamburg

21 Germany

22 mo.schoenfeld@uke.de

23 Tel: +49-40-7410-59140
24
25

26 4

27
28 **5 Word count**

29 6 5340 words
30
31

32 **8 Date and version**

33 9 First submission of manuscript: October 29, 2020

34 10 1. Resubmission of revised manuscript: August 10, 2021

35 11 2. Resubmission of revised manuscript: August 26, 2021
36
37

38 12
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

53 INTRODUCTION

54 Within the last decades, demographic change and increasing life expectancy have put older adults (≥ 60
55 years old as defined by the United Nations¹) in the focus of health care research. With increasing age, the
56 risk of chronic diseases and comorbidities rises resulting in a growing number of necessary treatments
57 (e.g. medication), and adherence to these treatments becomes crucial to reduce adverse reactions and
58 ensure safe and effective care. In this context, health literacy (HL), often defined as “the degree to which
59 individuals have the capacity to obtain, process, and understand basic health information and services
60 needed to make appropriate health decisions”², has been identified as a key influencing factor of
61 improving health-related behaviour in the elderly³. Accordingly, (elderly) people with low levels of HL use
62 health care more often and show higher rates of hospitalization than those with high levels of HL^{3,4}.

63 Research also confirmed low HL as a predictor of poor health outcomes linking lower HL to higher age⁵
64 ⁶, lower income⁵ and lower education^{3,7}. In addition, HL has been repeatedly linked to medication
65 adherence, commonly defined as “the extent to which a patient’s behaviour corresponds with the
66 prescribed medication dosing regime, including time, dosing and interval of medication intake”⁸.
67 Medication adherence (MA) has been the focus of this research since the number of medications taken
68 commonly increases with increasing age, making medication the most common form of therapy in the
69 elderly, often resulting in polypharmacy^{9,10}. Thus, MA still plays a crucial role in the elderly patient’s care.
70 However, research into the associations between HL and MA stays inconclusive¹¹⁻¹⁶. While multiple studies
71 reported (significantly) positive associations between HL and MA¹⁷⁻²¹, others reported (significantly)
72 negative associations^{22,23}.

73 Systematic reviews specifically conducted to analyse the relationship between HL and MA in the
74 elderly resulted in mixed findings as they often included studies with a variety of populations and measures
75 of HL^{12,16,24}. Older adults have commonly been examined as a homogenous group not taking into account
76 possible differences in levels of HL and MA between subgroups of age (e.g. 65-70 years old, 71-75 years
77 old, 76-80 years old, 85+ years old^{6,25}). In addition, reviews and meta-analyses examining the associations
78 between HL and MA in older age commonly included samples with a wide age range only focusing on the
79 mean age of samples. Since these samples often include (undisclosed) proportions of younger adults and
80 subgroups are not reported, results may not adequately reflect the relationship between HL and MA in
81 older adults^{24,26}. Also, reviews commonly included a low proportion of studies measuring HL with self-
82 reports. Instead, many reviews focused on the so-called legacy instruments of HL (i.e. REALM²⁷,
83 TOFHLA²⁸)^{12,24,26} including different measures and concepts of HL, which may lead to unknown bias^{15,26}. As
84 recently stated by Nguyen *et al.*²⁹, these often-deployed legacy tools may measure different aspects of
85 literacy and may not be appropriate to assess HL in older adults. Accordingly, limited HL was found to be
86 strongly associated with older age when measured with the TOFHLA (mainly assessing reading,
87 comprehension and numeracy skills²⁸) while limited HL had weak associations with older age³⁰ when
88 measured with the REALM (mainly assessing medical vocabulary²⁷).

89 As of late, these methodological shortcomings in research into HL have been increasingly recognized
90 leading to a broader discussion about the conceptualization and measurement of HL. Most recently,
91 researchers started concentrating on self-report measures of HL as new questionnaires from more
92 comprehensive concepts were developed (e.g. HLS-EU-Q³¹). Compared to performance-based measures,
93 self-reports of HL commonly offer a fast, easy, and inexpensive way to collect data and have a lower risk
94 of stigma³². Accordingly, self-reports present important advantages when assessing HL in different
95 populations and contexts as they can be applied more effortlessly. 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.

102

103 METHODS

104 A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic
105 Reviews and Meta-Analyses (PRISMA) guidelines³⁴. A checklist of PRISMA items can be found in online
106 supplementary file S1. This review was registered with the International Prospective Register of Systematic
107 Reviews (PROSPERO): CRD42019141028. The protocol is presented in online supplementary file S2.
108 Answers to reviewer comments are presented in online supplementary file S3.

109

110 Eligibility criteria

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

114 **Intervention.** No specific interventions were included in the criteria. Nevertheless, only studies that
115 assessed associations (e.g. correlation, effect size) between self-reported HL and MA were deemed
116 eligible. Studies that assessed HL solely with a performance-based test instrument (e.g. REALM²⁷,
117 TOFHLA²⁸) were excluded from this review.

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

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

123

124 Data sources and search strategy

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

1
2
3 136 In addition, reference lists from eligible articles were hand searched accordingly. All references were
4 137 subsequently imported into Endnote X8 reference management software for screening purposes.
5
6 138

7 139 **Study selection and screening**

8 140 After removal of duplicates, two raters (MSS, SPH) screened titles and abstracts of all remaining studies
9 141 for eligibility. A checklist was developed for this purpose. As many studies include HL only as a secondary
10 142 outcome and may thus not state it in the study's title or abstract, title/ abstract screening was conducted
11 143 more liberal. Accordingly, two raters (MSS, SPH) assessed the full texts of all previously screened studies
12 144 independently. Figure 1 shows reasons for study exclusion. In case of discrepancies, conflicts were
13 145 discussed until consensus was reached.
14
15 146

16 147 **Quality assessment**

17 148 The methodological quality of all studies included in this review was assessed using the NIH Quality
18 149 Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, NIH³⁵). Since only baseline
19 150 data from quantitative research was included, the NHLBI was deemed appropriate. The NHLBI contains 14
20 151 criteria mainly to assess the internal validity of a study. Each item was answered "yes" (if criterion was
21 152 met), "no" (if criterion was not met) or "cannot determine/ not applicable/ not reported". As the NHLBI is
22 153 not meant to assess the study quality by simply summing up its scores, an overall quality rating ("good",
23 154 "fair", "poor") for each study included a comprehensive and critical appraisal of each criterion as well as
24 155 the study as a whole.
25
26 156

27 157 **Data extraction and synthesis**

28 158 All relevant data was extracted by the first author with the help of a data extraction checklist containing
29 159 the following information: title, authors, year published, study design and setting, sample size, age groups,
30 160 definition and assessment of HL and MA, moderator and mediator effects (if available), statistical
31 161 measures to calculate associations between HL and MA, statistical significance if available.

32 162 As the studies showed heterogeneity due to differences in study design, participants, risk of bias, and
33 163 operationalization of HL and MA, a narrative synthesis was applied to analyse the studies thematically.
34
35 164

36 165 **Patient and public involvement**

37 166 Patients or the public were not involved in this study.
38
39 167

40 168 **RESULTS**

41 169 **Search results**

42 170 The literature search resulted in a total of 2,313 studies after removal of duplicates. After screening for
43 171 title and abstract another 1,769 studies were excluded based on exclusion criteria. Full texts of 544 studies
44 172 were screened and nine publications from eight studies met all eligibility criteria and were thus included
45 173 in this review (figure 1). Further details and reasons of exclusion are depicted in figure 1. The main reason
46 174 for study exclusion in the screening process was lack of self-reports of HL.
47
48 175
49 176

177 **Study characteristics**

178 Overall study characteristics are presented in table 1. All included publications were published between
179 2013 and 2020 with sample sizes between n=116 and n=12,159 (Median=293). The proportion of female
180 participants ranged from 33% to 100% (Median=53.6%). All studies adopted a cross-sectional design (5
181 survey studies). Three studies (four publications) were conducted in South Korea, and one study each in
182 China, USA, Pakistan, Israel, and Thailand. Studies were conducted across settings of tertiary care hospitals
183 (n=5), primary health care (n=1), private health care centres (n=1), community health care centres (n=1),
184 and clinics (n=1). All studies examined patients/adults with different types of (chronic) diseases:
185 hypertension (n=2), heart diseases (n=1), atrial fibrillation (n=2), osteoporosis (n=1), several chronic
186 diseases (n=3). Due to eligibility criteria restricting included samples to those with $\geq 66\%$ of older adults
187 (60 years of age and older), all studies focused on the elderly and only two studies also included patients
188 younger than 60 years (table 1). Five studies included samples with a higher proportion of women.

190 **Risk of bias**

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

195 **Health literacy – key findings**

196 In five publications from four studies³⁶⁻⁴⁰ self-reported HL was measured using a selection of questions
197 from the Brief Health Literacy Screen (BHLS⁴¹). The BHLS employs three to fifteen questions (e.g. “How
198 often do you have someone help you read hospital materials?”) to identify people with inadequate levels
199 of HL. Another study⁴² used the short version of the European Health Literacy Survey Questionnaire (HLS-
200 EU-Q) which was designed by the HLS-EU-Consortium based on a conceptual framework of HL³¹. One study
201 assessed HL with the Single Item Literacy Screener (SILS), which asks ““How often do you need to have
202 someone help when you read instructions, pamphlets, or other written material from your doctor or
203 pharmacy?”⁴³. Another two studies adopted the Functional, Communicative, and Critical Health Literacy
204 questionnaire (FCCHL) developed by Ishikawa *et al.*⁴⁴, a validated questionnaire that assesses three areas
205 of HL: functional HL, communicative HL, and critical HL.

206 Results on the overall levels of HL were mixed, yet a tendency towards limited HL (i.e. marginal, low,
207 inadequate) in the elderly was observable. While three publications from two studies^{36 37 40} only reported
208 mean levels of HL in samples patients aged 65 years and older, six studies reported different levels of HL
209 (e.g. marginal, low, or adequate HL). Three of these six studies^{39 42 45} used cut-offs recommended by the
210 original authors of the assessment instruments whereas three studies^{38 46 47} did not report how they
211 calculated HL scores. Five of these six studies^{39 42 45-47} found that a majority of the respective samples
212 reported limited HL levels (i.e. more people had low scores of HL; range from 62.6% to 92.5%,
213 Median=74.5%) whereas one study³⁸ found that a majority of the sample reported adequate levels of HL
214 (i.e. more people had high scores of HL; 76.9%).

216 **Medication adherence – key findings**

217 Four publications from three studies^{36 37 40 45} employed versions of the Morisky Medication Adherence
218 Scale (MMAS⁴⁸) to assess MA. The MMAS consists of four to eight questions asking about different aspects
219 of medication intake behaviour (e.g. “Do you sometimes forget to take your medication?”⁴⁸). One study⁴²

1
2
3 220 used the Medical Outcomes Study Specific Adherence Scale (MOS-SAS⁴⁹) which addresses MA (“How often
4 221 have you done each of the following in the past 4 weeks: Took medication as prescribed (on time without
5 222 skipping dosis?)”) as well as heart-healthy lifestyle behaviour (i.e. six preventive behaviours for coronary
6 223 heart disease, e.g. low-salt diet). One study³⁹ used a single-item adopted from Wu *et al.*⁵⁰ to assess MA
7 224 (“In the past week, have you forgotten to take your antithrombotic medication for various reasons?”).
8 225 Another study³⁸ adopted three questions from the Coronary Artery Risk Development in Young Adults
9 226 (CARDIA⁵¹) to assess MA (1. “In the past month, how often did you take your medications as the doctor
10 227 prescribed?”; 2. “In the past month, how often did you forget to take 1 or more of your prescribed
11 228 medications?”; 3. “In the past month, how often did you forget to take 1 or more of your prescribed
12 229 medications?”). MA was also assessed by the Medication Possession Ratio (MPR) in one study⁴⁶. The MPR
13 230 commonly represents the period during which a patient has an adequate amount of supply of his/her
14 231 medication available over a predefined amount of time (e.g. a year). One study assessed MA with the
15 232 Adherence to Refills and Medication Scale (ARMS⁵²) which assesses if a patient can correctly take and refill
16 233 his or her medication on schedule.

17 234 Overall, five publications from four studies^{36 37 39 45 46} found that a majority of the sample reported low
18 235 levels of MA (i.e. more non-adherers; range from 50.2% to 69.4%, Median=59.0%) while three studies^{38 42}
19 236 ⁴⁷ in contrast, found that a majority of the sample reported high levels of MA (i.e. more adherers; range
20 237 from 84.7% to 98.3%, Median=93.7%). One study reported a sample mean score of MA only⁴⁰.

Table 1. Overall summary of included studies

Authors, year	Setting, country	Sample				Disease	Risk of bias ¹
		N	Age (years), mean (±SD)	% Female	Age subgroups		
Lee <i>et al.</i> , 2013 ³⁶	Tertiary care hospitals, South Korea	n=293	65+ M=74.4 (6.3)	46.8%	NA	Chronic Diseases	fair
Lee <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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, NIH³⁵). NA: Not available/ not reported.

240 Age subgroups – key findings

241 Seven studies^{37-40 42 45 46} included in this review examined age subgroups for differences in HL and/or MA.
 242 All of these studies conducted subgroup analyses for differences in MA while only one of these studies⁴²
 243 examined differences in HL between age subgroups (e.g. 65-75 years old, 76-85 years old, >85 years old;
 244 table 2).

245 Overall, four studies^{37 42 45 46} found no significant differences in MA between age subgroups while one
 246 study³⁸ reported age as a significant predictor of medication nonadherence as younger patients (<65 years
 247 old) were more likely to be nonadherent compared to old/older patients (age groups 65-74 years old and
 248 75-84 years old) but not compared to the oldest (≥85 years old). One study⁴⁰ reported higher MA in 65-69-
 249 year-old adults compared to 70-79-year-old adults and ≥80-year-old adults. Another study³⁹ reported
 250 significant differences in adherence levels between age subgroups but did not confirm age as a significant
 251 predictor of medication nonadherence in multivariate analyses. Age was significantly associated with HL
 252 in one study⁴² as patients with limited HL were significantly older compared to those with adequate HL.
 253 However, regression analyses did not confirm age as a predictor of limited HL (table 2).
 254

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 <i>et al.</i> , 2013 ³⁶	NA	None conducted
Lee <i>et al.</i> , 2017 ³⁷	65-74 (57.0%) ≥75 (43.0%)	No significant differences in MA between age groups ($\chi^2=0.391$, $p=0.835$)
Lu <i>et al.</i> , 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 <ul style="list-style-type: none"> - 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 <ul style="list-style-type: none"> - 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 <i>et al.</i> , 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 <ul style="list-style-type: none"> - 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 <ul style="list-style-type: none"> - patients ≥85 years old (AOR (95% CI) = 0.86 (0.64-1.16), n.s.)
Saqlain <i>et</i>	65-75 (84.7%)	No significant differences in MA between age groups ($\chi^2=1.631$, $p=0.442$)

<i>al.</i> , 2019 ⁴⁵	76-85 (11.1%) >85 (4.2%)	
Seong <i>et al.</i> , 2019 ³⁹	65-70 (32.1%) 70-79 (45.5%) ≥80 (22.4%)	Adherence to medication significantly differed with respect to age ($\chi^2=15.15$, $p<0.001$) 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 <i>et al.</i> , 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 <i>et al.</i> , 2016 ⁴⁷	60-65 (52.7%) 66-70 (47.3%)	None conducted

255 **Notes:** NA: Not available/ not reported.

256

257 **Associations between health literacy and medication adherence**

258 Results of the analyses on associations between HL and MA are depicted in table 3. In addition, an
 259 overview of cutoffs and categories used for the measures of HL and MA in the included studies are
 260 depicted in online supplementary table S3. All studies conducted analyses on these associations. Overall,
 261 six publications from five studies^{36-38 40 45 47} reported positive and statistically significant associations
 262 between HL and MA while two studies^{42 46} did not find any significant associations, and one study³⁹
 263 reported mixed findings. In detail, one of two publications³⁶ from one study confirmed HL as the strongest
 264 predictor for MA in a hierarchical regression analysis while another publication³⁶ from this study found
 265 significantly positive associations between HL and MA but reported self-efficacy to be the strongest
 266 predictor for HL in their support vector machine (SVM) model. Another study⁴² found no significant
 267 differences between limited compared to adequate HL in (medication) nonadherent patients with
 268 coronary heart disease. However, the study reported that patients with limited HL were more likely to be
 269 nonadherent to secondary adherence measures (i.e. heart-healthy lifestyle, alcohol intake control,
 270 exercise, stress management) and suggested that changing how to take your pills may be easier than
 271 changing lifestyle behavior. In a study among ethnically diverse patients with atrial fibrillation³⁸, patients
 272 with inadequate levels of HL were significantly more likely to be nonadherent to medication than those
 273 with adequate levels of HL. In addition, the study found that included patients with self-reported physical
 274 inactivity (vs. physical activity), alcohol use (vs. no alcohol use), and diabetes mellitus were more likely to
 275 be nonadherent to medication, whereas patients with diagnosis of hypertension were less likely to be
 276 nonadherent to medication. A study on outpatients with hypertension⁴⁵ found positive and statistically

1
2
3 277 significant associations between HL and MA as well as a higher likelihood of patients with adequate levels
4 278 of HL to be adherent to medication compared to patients with inadequate levels of HL. In their multivariate
5 279 logistic regression, the same study found that in addition to adequate HL, self-reported good and
6 280 moderate subjective health as well as independence in activities of daily living were also independent
7 281 predictors of MA in the elderly. Another study³⁹ reported significant differences in adherence to
8 282 antithrombotic medication by levels of HL but did not confirm HL as a significant predictor for MA in older
9 283 adults. They concluded that a significant association between HL and MA might exist still since in their
10 284 univariate regression the rate of inadequate HL was higher in the group of nonadherent patients compared
11 285 to adherent patients. However, in their multivariate logistic regression, the authors³⁹ found only cognitive
12 286 impairment to be a significant predictor of medication nonadherence in older patients with atrial
13 287 fibrillation. One study⁴⁶ found no significant association between HL and MA in a population of female
14 288 Arab osteoporosis patients and found only self-reported income to be a significant predictor of adherence
15 289 in the conducted multivariate logistic regression. Another study⁴⁰ found significantly positive associations
16 290 between HL and MA. In their multiple regression analysis, the authors also found that income, number of
17 291 chronic diseases, vision problems, and HL were significant predictors of MA. One other study⁴⁷ analysed
18 292 the relationship between HL, MA, and blood pressure levels in primary care patients with hypertension
19 293 using a Structural Equation Modeling (SEM) approach, which supported the existence of a causal
20 294 relationship between these factors. Accordingly, HL had a positive but small statistically significant direct
21 295 effect on MA. Literacy and cognitive ability had the biggest direct effects on both HL and MA. Additionally,
22 296 HL had the biggest significantly negative direct effect on blood pressure levels (i.e. the higher the HL, the
23 297 lower the blood pressure level). Based on the SEM, the authors of this study⁴⁷ suggested a mediator effect
24 298 of HL on MA, even though no analysis was conducted. None of the other studies performed mediator
25 299 and/or moderator analyses concerning HL and/or MA and other factors
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 300
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

For peer review only

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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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)

1						
2						
3	Saqlain <i>et al.</i> , 2019 ⁴⁵	n=262, 65+ years	SILS	MMAS-4	n=98 (37.4%) patients had adequate HL	Positive and statistically significant associations between HL and MA ($\chi^2=24.356$, $p<0.001$)
4						
5		M=NA			n=102 (38.9%) patients were adherent to medication	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), $p<0.001$)
6						
7		Outpatients with				
8		hypertension from tertiary				
9		health care centres in				
10		Islamabad, Pakistan				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), $p<0.002$)
11	Seong <i>et al.</i> , 2019 ³⁹	n=277, 65+ years	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	Positive and statistically significant associations between HL and MA ($\chi^2=22.00$, $p<0.001$)
12		M=74.2 (7.2)				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), $p=0.002$)
13					n=139 (50.2%) patients were nonadherent to medication	
14		Outpatients with atrial				
15		fibrillation undergoing				
16		antithrombotic therapy in				
17		tertiary general hospital in				
18		South Korea			Significant differences in MA between age subgroups ($p<0.001$)	
19						
20	Shehadeh- Sheeny <i>et al.</i> , 2013 ⁴⁶	n=303, 60+ years	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	No significant associations between MA and HL ($p=0.44$)
21						
22		M= 71 (6.04)				46.7% of patients with high HL were more adherent to medication compared to 35.9% of patients with low HL
23						
24		Female Arab patients			n=125 (41.3%) patients had high MA	In multivariate logistic regression only self-reported income was a significant predictor of MA (OR (95% CI) = 1.26 (1.01-1.58), $p=0.037$)
25		with osteoporosis				
26		from three clinics in Israel				
27	Song & Park, 2020 ⁴⁰	n=116, 65+ years	BHLS 15 questions	MMAS-8	Mean HL was 42.4 (6.6)	HL positively correlated with MA ($r=0.42$, $p<0.001$)
28						
29		M=72.7 (6.1)			Mean MA was at a medium level (M=4.3 (2.2))	In multiple regression analysis HL was significant predictor of MA in multiple regression ($\beta=0.23$, $p<0.001$)
30						
31		Community-dwelling older				Other significant predictors of MA were income ($\beta=0.35$, $p<0.001$), number of chronic diseases ($\beta=-0.33$, $p<0.001$), and vision problems ($\beta=-0.32$, $p<0.001$)
32		adults in health care centre, South Korea				
33						
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						

1						
2						
3	Wannasirikul	n=600,	FCCHL	ARMS	Mean HL was 40.0 (10.4)	SEM supports causal relationship between HL, MA, and blood pressure
4	<i>et al.</i> , 2016 ⁴⁷	60-70 years				HL had a significantly positive direct effect on MA in SEM ($\beta=0.08$, $p<0.05$)
5		M=65.3			HL levels were inadequate, marginal, and adequate for 48.7%, 43.8%, and 7.5% of patients, respectively	Cognitive ability ($\beta=0.22$, $p<0.05$) and literacy ($\beta=0.46$, $p<0.05$) had biggest and significantly positive direct effect on MA
6		Patients with hypertension from primary health care centre in Sa Kaeo Province, Thailand			MA was good for 98.3% of patients	Literacy ($\beta=0.15$, $p<0.05$) and cognitive ability ($\beta=0.52$, $p<0.05$) had biggest and significantly positive direct effect on HL
7						HL had biggest significantly negative direct effect on blood pressure level ($\beta=-0.14$, $p<0.05$)
8						MA had a significantly negative direct effect on blood pressure level ($\beta=-0.02$, $p<0.05$)
9						
10						Results suggest mediator effect of HL on MA
11						
12						

301 **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
 302 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.

303 DISCUSSION

304 The aim of this study was to systematically examine the associations of HL and MA in older adults. Although
305 research on HL and MA in older adults has rapidly increased in the last years, mixed results are a common
306 denominator in this area^{15 53}. Accordingly, previous systematic reviews resulted in a range of conclusions
307 as they included a variety of HL concepts, different (younger) age groups, and a range of methodologically
308 different instruments (self-reports as well as performance-based measures) to assess HL^{12 16 24 26 53}. To our
309 knowledge, this is the first systematic review to focus specifically on self-reported HL while explicitly
310 including studies with samples of older adults. We found that only few validated instruments of self-
311 reported HL are used and that most studies still rely on legacy measures to assess HL even though their
312 use has been criticized repeatedly and self-reports of HL offer a range of advantages³². Studies included in
313 our review mostly assessed MA in older adults through self-reports, even though a wide range of tools is
314 known^{54 55}.

315 In this review, results appear to be more consistent in contrast to previous reviews^{15 16} as many
316 included studies reported positive and statistically significant associations between HL and MA. This could
317 be explained by the fact that only older adults (at least 66% of older adults in samples, not based on the
318 samples' mean age) were examined in the included studies and associations in this group may be more
319 prominent compared to studies that also include subgroups of younger people. One review²⁴ for example
320 aimed to review literature that examined HL and MA in older adults with cardiovascular disease or
321 diabetes. Included studies in the review had to assess HL with legacy instruments only and had to include
322 samples of participants with a "[...] mean age [of] at least 50 years or with at least a third of participants
323 aged 50 years or older [...]" and could not confirm an association between HL and MA. As stated earlier,
324 inclusion of younger participants may have resulted in unknown bias from age. Yet another bias may have
325 resulted from the utilization of legacy measures with different conceptualizations of HL since the REALM
326 and TOFHLA, two of the most prominent legacy tools of HL, are confirmed to assess different aspects of
327 literacy rather than HL and may thus be differently impacted by a person's intelligence²⁹. Accordingly, Loke
328 *et al.* stated in their review that functional measures of HL may not be adequate and "[n]ew methods of
329 measuring health literacy beyond the functional level are needed [...]".

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

1
2
3 346 reported HL are still widely lacking, we need more research to explore and develop comprehensive
4 347 theories in this area.

5 348 Six studies^{38 39 42 45-47} included in this review found that a majority of participants in the respective
6 349 samples reported limited (i.e. inadequate, low, marginal) HL. This is consistent with other research that
7 350 showed that older people commonly reach only low levels of self-reported health literacy^{3 25 33} even though
8 351 this research is very scarce. HL was measured by versions of four different self-reports (BHLS^{41 56}, HLS-EU-
9 352 Q³, SILS⁴³, FCCHL⁴⁴). This shows that self-reporting HL measures are still rarely utilized when examining
10 353 older adults, even though the Health literacy Tool Shed⁵⁷ lists 29 self-report instruments for HL in English
11 354 alone (58 without language restrictions).

12 355 MA was assessed through self-reports in all but one of the included studies^{36-40 42 45 47}. Nevertheless,
13 356 we recommend a more detailed description of operationalization of MA as many studies still use the
14 357 concepts of adherence and compliance interchangeably. Interestingly, we had to exclude many studies
15 358 from this review even though they assessed some form of adherence, because they only included
16 359 measures of general preventive behaviour (e.g. physical activity) and not MA. However, the use of such
17 360 secondary adherence measures might be a promising approach to get a more comprehensive picture of
18 361 adherence in older adults⁵⁵. Especially a multi-method approach could be helpful since self-reported
19 362 adherence may also be affected by cognitive bias and/or social desirability in older adults. As such, the
20 363 utilization of both direct (e.g. laboratory measures) and indirect (e.g. self-reports) measures of
21 364 adherence^{55 58} may help to get a better understanding of adherence and its associations with self-reported
22 365 HL in older adults. A number of studies in this review also included measures of secondary prevention (e.g.
23 366 physical activity, heart-healthy lifestyle behavior) as well as other factors (e.g. income, cognitive ability)
24 367 providing further knowledge on possible confounders in the mechanisms between HL and MA.
25 368 Accordingly, several studies confirmed multiple other factors as predictors for MA (e.g., health status^{37 38}
26 369 ⁴⁵, income^{40 46}, physical activity^{38 45}, cognitive ability^{39 47}) and/ or HL (e.g., cognitive ability⁴⁷, stress
27 370 management⁴²). In a recent systematic review and meta-analysis by Lim et al.⁵⁹, the authors examined the
28 371 associations between physical activity and HL and found that older adults with inadequate levels of HL
29 372 were “[...] less likely [...] to report engaging in physical activity [...]” than those with adequate HL, showing
30 373 the importance of also addressing secondary adherence measures in future research in this area. Notably,
31 374 their review also included younger adults (samples with mean age ≥55 years) and different of HL measures
32 375 (legacy measures and self-reports).

33 376 Even though we also encourage researchers to assess HL with a multi-method approach (e.g.
34 377 subjective and objective instruments), we suggest a more rigorous differentiation in analysis and
35 378 interpretation when comparing HL measures that are based on different concepts (e.g. legacy tools and
36 379 self-reports). This may also help to clarify further the associations between self-reported HL and literacy
37 380 as measured by legacy instruments. As stated by Nguyen *et al.*²⁹, a separation in analyses of objective and
38 381 subjective measures of HL as well as a closer alignment of HL theory and measurement could help clarify
39 382 the relationship between HL and MA. This idea was also supported by one of the studies⁴⁰ included in this
40 383 review, which aimed at comparing two different measures of HL (self-report vs. legacy measure). The
41 384 authors found that even though both measures were significantly and positively correlated to MA, only
42 385 the self-report was a significant predictor for MA in older adults suggesting that self-reports may be more
43 386 fitting to assess HL when predicting MA since “[...] assessing older adults’ experiences of limited health
44 387 literacy is more appropriate for catching any decreased medication adherence [...]”.

1
2
3 388 This review additionally confirms that age subgroup analyses are conducted very rarely for self-
4 389 reported HL but quite often for MA. This may result from the fact that research on MA in the elderly is
5 390 traditionally older than research on HL in the elderly and with regard to HL most studies still treat older
6 391 people as a homogenous group²⁵. Most studies in this review did not find any significant associations
7 392 between age and MA and only two studies^{38 40} reported significant differences in MA between age
8 393 subgroups. Accordingly, one study³⁸ reported that young/ young-old people (21-65 years old) were more
9 394 likely not to adhere to their medication compared to old/older adults (65-84 years old) but not oldest
10 395 adults (≥ 85 years old). A second study⁴⁰ reported higher MA in 65-69-year-old adults compared to
11 396 older/oldest adults (70-90 years old). Not surprisingly, only one study conducted analyses on the
12 397 relationship between age and HL⁴², showing that patients with limited HL were significantly older
13 398 compared to those with adequate HL. Even though generalizability is very limited, these results reveal the
14 399 necessity for more differentiated analyses (e.g. of subgroups) in future HL and MA research on older
15 400 adults. In context of demographic change and increasing life expectancy, more differentiated analyses
16 401 could help to understand specific needs and barriers of elderly (patient) populations with different chronic
17 402 diseases. Importantly, definitions of *old age* are often inconsistent and include people from ages 60, 65,
18 403 or 70 years and over. These dissimilarities in the definitions of old age may result from differences in
19 404 cultural and/or economic standards (e.g. USA vs. Asia) and often manifest in different demographic
20 405 changes and/or different life expectancies thus resulting in a different quality of health care in groups of
21 406 older adults. Consequently, when looking at older adults' health care and health outcomes, it is critical to
22 407 include contextual aspects such as cultural or economic standards.

23 408 Studies in this review show some inconsistencies in the use of cutoffs, use, and wording of HL levels.
24 409 Of all included studies, six studies^{38 39 42 45-47} reported categories of HL (e.g. adequate) of which only three³⁹
25 410 ^{42 45} reported cutoffs for these categories. Three publications^{36 37 40} from two studies reported neither
26 411 categories nor cutoffs for HL and only five publications^{36 37 39 40 47} from four studies reported mean values
27 412 of HL. For example, Shehadeh-Sheeny et al. calculated scores for low, medium, and high levels of HL while
28 413 Wannasirikul et al. calculated scores for adequate, marginal, and inadequate HL levels even though no
29 414 cutoffs were reported/available by neither the authors nor the FCCHL measure both studies used. The
30 415 inconsistent use of cutoffs and wording may indicate a lack of certainty and experience in the application
31 416 of self-reports enhancing the call for more differentiated research and the development of easy-to-use
32 417 but still valid tools.

33 418

34 419 **Strength and limitations**

35 420 The strengths of this study include the exhaustive methodology and comprehensive search strategy that
36 421 were used. As we followed a strict screening procedure, we are confident that we found all eligible studies.
37 422 Since we excluded all studies that measured HL with performance-based instruments, we aimed to reduce
38 423 bias resulting from fundamental differences in constructs and concepts. Although we see this exclusion as
39 424 a considerable advantage, we cannot eliminate the possibility of bias still resulting from theoretical or
40 425 practical differences in self-reports as some of them are built on more complex conceptual frameworks
41 426 than others. Additionally, there are advantages in assessing HL in older adults with self-reports since they
42 427 reduce the possible bias of performance-based measures resulting from fear of stigma and/or (time)

1
2
3 428 pressure. Nevertheless, we recognize the inherent limitations of self-reporting tools that may also have
4 429 biased our results.

5
6 430 Other limitations should be considered. All studies included in this review were cross-sectional, thus
7 431 we cannot determine any direction of causality. The fair to poor methodological quality of the included
8 432 studies may also increase the risk of (unknown) bias. Given the heterogeneity of the studies, a meta-
9 433 analysis (e.g. pooled odds ratios) could not be conducted, thus limiting further understanding of the
10 434 relationship between HL and MA in older adults. Additionally, our search strategy in this review limited
11 435 included studies to English and German, which could bias results due to missing research in other
12 436 languages. Finally, we were not able to include EMBASE as a database in our search. Even though, we are
13 437 very confident that we did not miss a substantial amount of literature, this must be considered as a
14 438 limitation of this review.

15
16
17
18
19 439

20 21 440 **CONCLUSIONS**

22 441 In this review, self-reported HL and MA in older adults show a rather straightforward positive association.
23 442 While previous research on HL and MA in older adults did not always find clear associations, many studies
24 443 included in this review reported significantly positive associations between HL and MA. In addition, HL
25 444 plays an important role as a predictor of MA in older adults as several studies in this review could confirm.
26 445 However, other factors (e.g. cognitive ability) appear equally important in predicting MA in older adults,
27 446 and future studies should also focus on secondary adherence measures (e.g. physical activity) when
28 447 examining the associations between HL and MA in the elderly. Finally, study heterogeneity and
29 448 methodological weaknesses reveal a definitive need for more differentiated research regarding different
30 449 definitions, concepts, and measures of HL and MA as well as longitudinal research designs and studies that
31 450 analyse age subgroups in older adults.

32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 451 **Acknowledgements**

4 452 We would like to thank Dr. rer. biol. hum. Laura Inhestern for her advice during the preparation of the
5 453 search for this review.
6 454

7 455 **Author Contributions**

8 456 All Authors were involved in the design and planning of the review. MSS prepared, performed, and
9 457 redefined the searches after consultation with SPH and CB. MSS and SPH performed screening and data
10 458 extraction with the help of CB in case of disagreements or discussion. All authors contributed to the data
11 459 analysis and interpretation. MSS wrote the first draft which was critically revised by SPH and CB.
12 460

13 461 **Ethics Approval Statement**

14 462 This study does not involve human participants, as it is a systematic review.
15 463

16 464 **Funding**

17 465 This research received no specific grant from any funding agency in the public, commercial or not-for-
18 466 profit sectors.
19 467

20 468 **Competing interests**

21 469 None declared.
22 470

23 471 **Patient consent**

24 472 Not required.
25 473

26 474 **Provenance and peer review**

27 475 Not commissioned; externally peer reviewed.
28 476

29 477 **Data sharing statement**

30 478 All data relevant to the study are included in the article or uploaded as supplementary information.
31 479

32 480 **Open Access**

33 481 This is an open access article distributed in accordance with the Creative Commons Attribution Non
34 482 Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work
35 483 non-commercially, and license their derivative works on different terms, provided the original work is
36 484 properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial.
37 See: <http://creativecommons.org/licenses/by-nc/4.0/>.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

485 **REFERENCES**

- 486 1 United Nations DoEaSA, Population Division. World Population Ageing 2019: Highlights
487 (ST/ESA/SER.A/430) 2020.
- 488 2 Ratzan SC, Parker RM. Health literacy - identification and response. *J Health Commun* 2006;**11**:713-
489 5.doi:10.1080/10810730601031090
- 490 3 HLS-EU Consortium. Comparative Report on Health Literacy in Eight EU Member States. The European
491 Health Literacy Project 2009–2012. Vienna: Ludwig Boltzmann Institute for Health Promotion Research
492 2012.
- 493 4 Berkman ND, Sheridan SL, Donahue KE, et al. Low health literacy and health outcomes: an updated
494 systematic review. *Ann Intern Med* 2011;**155**:97-107.doi:10.7326/0003-4819-155-2-201107190-00005
- 495 5 Chesser AK, Keene Woods N, Smothers K, et al. Health Literacy and Older Adults: A Systematic Review.
496 *Gerontol Geriatr Med* 2016;**2**:2333721416630492.doi:10.1177/2333721416630492
- 497 6 Vogt D, Schaeffer D, Messer M, et al. Health literacy in old age: results of a German cross-sectional
498 study. *Health Promot Int* 2018;**33**:739-47.doi:10.1093/heapro/dax012
- 499 7 Wolf MS, Feinglass J, Thompson J, et al. In search of 'low health literacy': threshold vs. gradient effect
500 of literacy on health status and mortality. *Soc Sci Med* 2010;**70**:1335-
501 41.doi:10.1016/j.socscimed.2009.12.013
- 502 8 Gast A, Mathes T. Medication adherence influencing factors—an (updated) overview of systematic
503 reviews. *Systematic Reviews* 2019;**8**:1-17.doi:10.1186/s13643-019-1014-8
- 504 9 Hoel RW, Connolly RMG, Takahashi PY. Polypharmacy Management in Older Patients. *Mayo Clinic*
505 *Proceedings* 2021;**96**:242-56.doi:10.1016/j.mayocp.2020.06.012
- 506 10 Chiatti C, Bustacchini S, Furneri G, et al. The economic burden of inappropriate drug prescribing, lack
507 of adherence and compliance, adverse drug events in older people: a systematic review. *Drug Saf*
508 2012;**35 Suppl 1**:73-87.doi:10.1007/BF03319105
- 509 11 Huang YM, Shiyabola OO, Smith PD. Association of health literacy and medication self-efficacy with
510 medication adherence and diabetes control. *Patient Prefer Adherence* 2018;**12**:793-
511 802.doi:10.2147/PPA.S153312
- 512 12 Martins NFF, Abreu DPG, Silva BTD, et al. Functional health literacy and adherence to the medication
513 in older adults: integrative review. *Rev Bras Enferm* 2017;**70**:868-74.doi:10.1590/0034-7167-2016-0625
- 514 13 Park NH, Song MS, Shin SY, et al. The effects of medication adherence and health literacy on health-
515 related quality of life in older people with hypertension. *Int J Older People Nurs*
516 2018;**13**:e12196.doi:10.1111/opn.12196
- 517 14 Roh YH, Koh YD, Noh JH, et al. Effect of health literacy on adherence to osteoporosis treatment
518 among patients with distal radius fracture. *Arch Osteoporos* 2017;**12**:42.doi:10.1007/s11657-017-0337-0
- 519 15 Zhang NJ, Terry A, McHorney CA. Impact of health literacy on medication adherence: a systematic
520 review and meta-analysis. *Ann Pharmacother* 2014;**48**:741-51.doi:10.1177/1060028014526562
- 521 16 Ostini R, Kairuz T. Investigating the association between health literacy and non-adherence.
522 *International journal of clinical pharmacy* 2014;**36**:36-44.doi:10.1007/s11096-013-9895-4
- 523 17 Lindquist LA, Go L, Fleisher J, et al. Relationship of health literacy to intentional and unintentional
524 non-adherence of hospital discharge medications. *J Gen Intern Med* 2012;**27**:173-8.doi:10.1007/s11606-
525 011-1886-3
- 526 18 Wolf MS, Davis TC, Osborn CY, et al. Literacy, self-efficacy, and HIV medication adherence. *Patient*
527 *Educ Couns* 2007;**65**:253-60.doi:10.1016/j.pec.2006.08.006
- 528 19 Kripalani S, Gatti ME, Jacobson TA. Association of age, health literacy, and medication management
529 strategies with cardiovascular medication adherence. *Patient Educ Couns* 2010;**81**:177-
530 81.doi:10.1016/j.pec.2010.04.030
- 531 20 Bauer AM, Schillinger D, Parker MM, et al. Health literacy and antidepressant medication adherence
532 among adults with diabetes: the diabetes study of Northern California (DISTANCE). *J Gen Intern Med*
533 2013;**28**:1181-7.doi:10.1007/s11606-013-2402-8

- 1
2
3 534 21 Mayo-Gamble TL, Mouton C. Examining the Association Between Health Literacy and Medication
4 535 Adherence Among Older Adults. *Health Commun* 2018;**33**:1124-30.doi:10.1080/10410236.2017.1331311
5 536 22 Mosher HJ, Lund BC, Kripalani S, et al. Association of health literacy with medication knowledge,
6 537 adherence, and adverse drug events among elderly veterans. *J Health Commun* 2012;**17 Suppl 3**:241-
7 538 51.doi:10.1080/10810730.2012.712611
8 539 23 Fang MC, Machtinger EL, Wang F, et al. Health literacy and anticoagulation-related outcomes among
9 540 patients taking warfarin. *J Gen Intern Med* 2006;**21**:841-6.doi:10.1111/j.1525-1497.2006.00537.x
10 541 24 Loke YK, Hinz I, Wang X, et al. Systematic review of consistency between adherence to cardiovascular
11 542 or diabetes medication and health literacy in older adults. *Ann Pharmacother* 2012;**46**:863-
12 543 72.doi:10.1345/aph.1Q718
13 544 25 Vogt D, Berens EM, Schaeffer D. [Health Literacy in Advanced Age]. *Gesundheitswesen* 2020;**82**:407-
14 545 12.doi:10.1055/a-0667-8382
15 546 26 Geboers B, Brainard JS, Loke YK, et al. The association of health literacy with adherence in older
16 547 adults, and its role in interventions: a systematic meta-review. *BMC Public Health*
17 548 2015;**15**:903.doi:10.1186/s12889-015-2251-y
18 549 27 Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened
19 550 screening instrument. *Fam Med* 1993;**25**:391-5
20 551 28 Parker RM, Baker DW, Williams MV, et al. The test of functional health literacy in adults: a new
21 552 instrument for measuring patients' literacy skills. *J Gen Intern Med* 1995;**10**:537-
22 553 41.doi:10.1007/BF02640361
23 554 29 Nguyen TH, Paasche-Orlow MK, McCormack LA. The State of the Science of Health Literacy
24 555 Measurement. *Stud Health Technol Inform* 2017;**240**:17-33
25 556 30 Kobayashi LC, Wardle J, Wolf MS, et al. Aging and Functional Health Literacy: A Systematic Review
26 557 and Meta-Analysis. *J Gerontol B Psychol Sci Soc Sci* 2016;**71**:445-57.doi:10.1093/geronb/gbu161
27 558 31 Sorensen K, Van den Broucke S, Pelikan JM, et al. Measuring health literacy in populations:
28 559 illuminating the design and development process of the European Health Literacy Survey Questionnaire
29 560 (HLS-EU-Q). *BMC Public Health* 2013;**13**:948.doi:10.1186/1471-2458-13-948
30 561 32 Nguyen TH, Paasche-Orlow MK, McCormack LA. The state of the science of health literacy
31 562 measurement. *Information Services & Use* 2017;**37**:189--203.doi:10.3233/isu-170827
32 563 33 Berens EM, Vogt D, Messer M, et al. Health literacy among different age groups in Germany: results
33 564 of a cross-sectional survey. *BMC Public Health* 2016;**16**:1151.doi:10.1186/s12889-016-3810-6
34 565 34 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-
35 566 analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.doi:10.1371/journal.pmed.1000097
36 567 35 National Heart, Lung, and Blood Institute. Quality Assessment Tool for Observational Cohort and
37 568 Cross-Sectional Studies. 2014. Available from: [https://www.nhlbi.nih.gov/health-pro/guidelines/in-](https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort)
38 569 [develop/cardiovascular-risk-reduction/tools/cohort](https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort).
39 570 36 Lee SK, Kang BY, Kim HG, et al. Predictors of medication adherence in elderly patients with chronic
40 571 diseases using support vector machine models. *Healthc Inform Res* 2013;**19**:33-
41 572 41.doi:10.4258/hir.2013.19.1.33
42 573 37 Lee YM, Yu HY, You MA, et al. Impact of health literacy on medication adherence in older people with
43 574 chronic diseases. *Collegian* 2017;**24**:11-8.doi:10.1016/j.colegn.2015.08.003
44 575 38 Reading SR, Black MH, Singer DE, et al. Risk factors for medication non-adherence among atrial
45 576 fibrillation patients. *BMC Cardiovasc Disord* 2019;**19**:38.doi:10.1186/s12872-019-1019-1
46 577 39 Seong HJ, Lee K, Kim BH, et al. Cognitive Impairment Is Independently Associated with Non-
47 578 Adherence to Antithrombotic Therapy in Older Patients with Atrial Fibrillation. *Int J Environ Res Public*
48 579 *Health* 2019;**16**.doi:10.3390/ijerph16152698
49 580 40 Song MS, Park S. Comparing two health literacy measurements used for assessing older adults'
50 581 medication adherence. *J Clin Nurs* 2020;**29**:4313-20.doi:10.1111/jocn.15468
51
52
53
54
55
56
57
58
59

- 1
2
3 582 41 Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy.
4 583 *Fam Med* 2004;**36**:588-94
- 5 584 42 Lu M, Ma J, Lin Y, et al. Relationship between patient's health literacy and adherence to coronary
6 585 heart disease secondary prevention measures. *J Clin Nurs* 2019;**28**:2833-43.doi:10.1111/jocn.14865
- 7 586 43 Morris NS, MacLean CD, Chew LD, et al. The Single Item Literacy Screener: evaluation of a brief
8 587 instrument to identify limited reading ability. *BMC Fam Pract* 2006;**7**:21.doi:10.1186/1471-2296-7-21
- 9 588 44 Ishikawa H, Takeuchi T, Yano E. Measuring functional, communicative, and critical health literacy
10 589 among diabetic patients. *Diabetes Care* 2008;**31**:874-9.doi:10.2337/dc07-1932
- 11 590 45 Saqlain M, Riaz A, Malik MN, et al. Medication Adherence and Its Association with Health Literacy
12 591 and Performance in Activities of Daily Livings among Elderly Hypertensive Patients in Islamabad,
13 592 Pakistan. *Medicina (Kaunas)* 2019;**55**.doi:10.3390/medicina55050163
- 14 593 46 Shehadeh-Sheeny A, Eilat-Tsanani S, Bishara E, et al. Knowledge and health literacy are not
15 594 associated with osteoporotic medication adherence, however income is, in Arab postmenopausal
16 595 women. *Patient Educ Couns* 2013;**93**:282-8.doi:10.1016/j.pec.2013.06.014
- 17 596 47 Wannasirikul P, Termsirikulchai L, Sujirarat D, et al. Health Literacy, Medication Adherence, and
18 597 Blood Pressure Level among Hypertensive Older Adults Treated at Primary Health Care Centers.
19 598 *Southeast Asian J Trop Med Public Health* 2016;**47**:109-20
- 20 599 48 Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of
21 600 medication adherence. *Med Care* 1986;**24**:67-74.doi:10.1097/00005650-198601000-00007
- 22 601 49 Sherbourne CD, Hays RD, Ordway L, et al. Antecedents of adherence to medical recommendations:
23 602 results from the Medical Outcomes Study. *J Behav Med* 1992;**15**:447-68.doi:10.1007/BF00844941
- 24 603 50 Wu JR, DeWalt DA, Baker DW, et al. A single-item self-report medication adherence question predicts
25 604 hospitalisation and death in patients with heart failure. *J Clin Nurs* 2014;**23**:2554-
26 605 64.doi:10.1111/jocn.12471
- 27 606 51 Cutter GR, Burke GL, Dyer AR, et al. Cardiovascular risk factors in young adults. The CARDIA baseline
28 607 monograph. *Control Clin Trials* 1991;**12**:1S-77S.doi:10.1016/0197-2456(91)90002-4
- 29 608 52 Kripalani S, Risser J, Gatti ME, et al. Development and evaluation of the Adherence to Refills and
30 609 Medications Scale (ARMS) among low-literacy patients with chronic disease. *Value Health* 2009;**12**:118-
31 610 23.doi:10.1111/j.1524-4733.2008.00400.x
- 32 611 53 Miller TA. Health literacy and adherence to medical treatment in chronic and acute illness: A meta-
33 612 analysis. *Patient Educ Couns* 2016;**99**:1079-86.doi:10.1016/j.pec.2016.01.020
- 34 613 54 Lam WY, Fresco P. Medication Adherence Measures: An Overview. *Biomed Res Int*
35 614 2015;**2015**:217047.doi:10.1155/2015/217047
- 36 615 55 Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment
37 616 adherence. *Med Pharm Rep* 2019;**92**:117-22.doi:10.15386/mpr-1201
- 38 617 56 Chew LD, Griffin JM, Partin MR, et al. Validation of screening questions for limited health literacy in a
39 618 large VA outpatient population. *J Gen Intern Med* 2008;**23**:561-6.doi:10.1007/s11606-008-0520-5
- 40 619 57 Health Literacy Tool Shed [Internet]. Boston University, Research Triangle Institute International.
41 620 [cited 08/17/2020]. Available from: <https://healthliteracy.bu.edu>.
- 42 621 58 McRae-Clark AL, Baker NL, Sonne SC, et al. Concordance of Direct and Indirect Measures of
43 622 Medication Adherence in A Treatment Trial for Cannabis Dependence. *J Subst Abuse Treat* 2015;**57**:70-
44 623 4.doi:10.1016/j.jsat.2015.05.002
- 45 624 59 Lim ML, van Schooten KS, Radford KA, et al. Association between health literacy and physical activity
46 625 in older people: a systematic review and meta-analysis. *Health Promot Int*
47 626 2020;**daaa072**.doi:10.1093/heapro/daaa072

54 627
55
56 **Figure 1. PRISMA Flow Diagram**

57 Note: *only for samples that not exclusively focus on elders
58
59

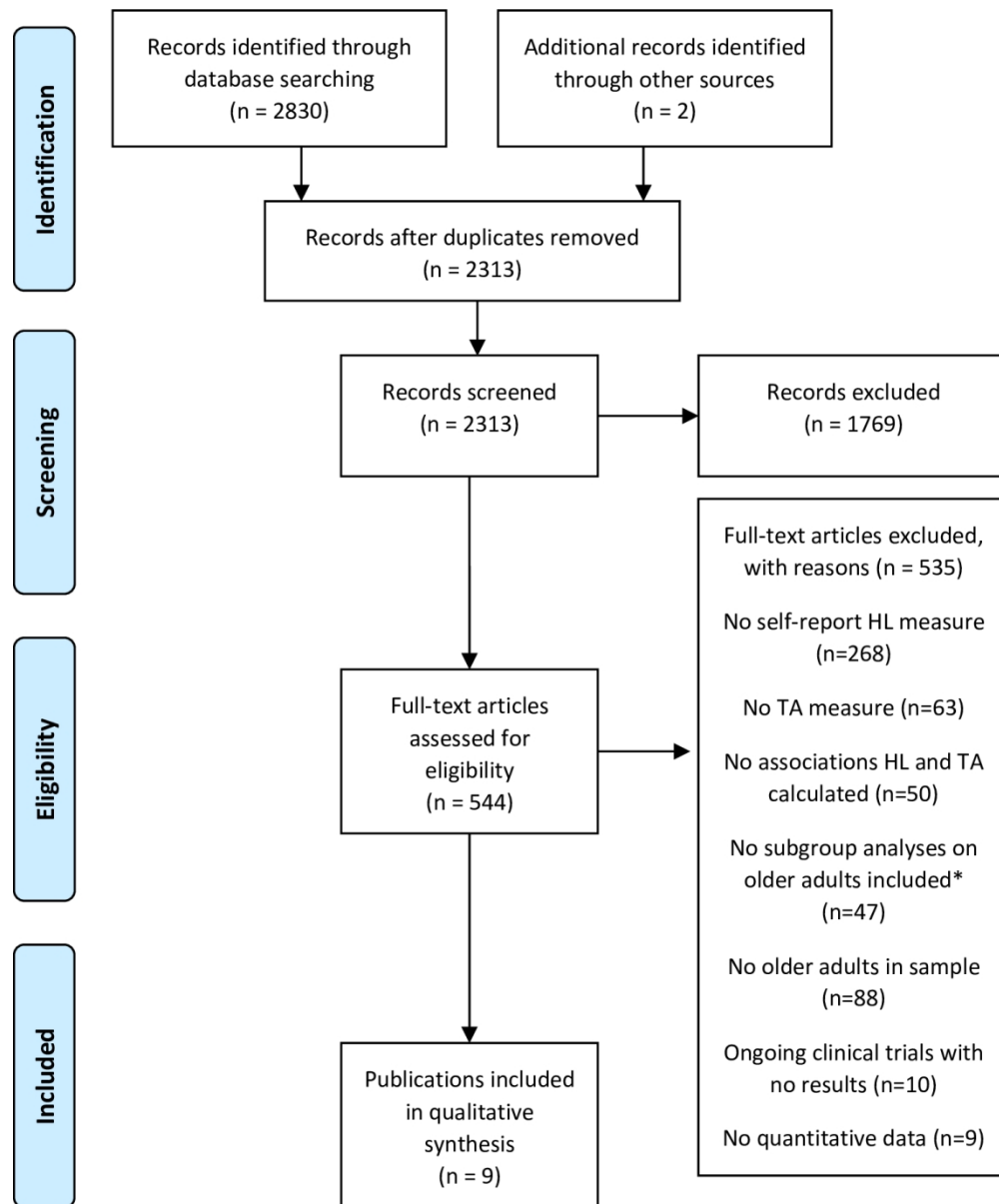


Figure 1. PRISMA Flow Diagram Note: *only for samples that not exclusively focus on elders

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

Page 1 of 2

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.

Page 2 of 2

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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, Department 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

1
2
3
4 Reviewer(s)' Comments to Author:
5

6 **Reviewer: 1**
7

8 Comments to the Author:
9

10 The definition of each measurement must be clarified in the study method, and if the measurement method is
11 different, the study needs to be corrected with major drawbacks. Also, please new findings of the results from
12 this study should be described clearly in the abstracts and conclusions.

13 **Our answer: Thank you very much for taking the time to review our manuscript and for your comments.**
14 **Indeed, we agree that the definition of measurements might not be clear enough and have corrected this**
15 **accordingly. We now define medication adherence as such and excluded treatment adherence from our**
16 **review since we originally aimed to review the associations between medication adherence and health**
17 **literacy as represented by our search strategy and methods.**
18 **Also, we added information of our results to the abstract and conclusion sections.**
19

20
21 **Reviewer: 2**
22

23 Comments to the Author:
24

25 Thank you for opportunity to review this paper. This systematic review aimed to explore the association be-
26 tween self-reported health literacy and treatment adherence in older adults. This study seemed to be well fol-
27 lowed the guideline by PRISMA.

28 **Our answer: Thank you very much for your comments and for taking the time to review our manuscript. We**
29 **appreciate it very much!**
30

31 The authors emphasized that this review is the first study on the association between health literacy and treat-
32 ment adherence in older adults. However, it is difficult to agree to the authors' statement.

33 **Our answer: Thank you for this important comment. Another reviewer pointed out a similar aspect. We com-**
34 **pletely agree with you. We did indeed aim to review the associations between health literacy and medication**
35 **adherence, not treatment adherence, as represented in our search strategy and methods. You are correct**
36 **that we did not include studies focusing on treatment adherence but only those that focused on medication**
37 **adherence. Using the definition and wording of treatment adherence, we wished to address a broader audi-**
38 **ence. As treatment adherence includes medication adherence, we used both definitions somewhat inter-**
39 **changeably, but now realize that this leads to confusion and duplication. Accordingly, we deleted references**
40 **to treatment adherence in all cases we actually meant medication adherence and changed the definition to**
41 **medication adherence. Thank you again for your comment. (lines 64-65)**
42
43

44 In introduction section, the authors presented the definition of treatment adherence by WHO. Namely, the ex-
45 tent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, cor-
46 responds with agreed recommendations from a health care provider" From this perspective, the authors should
47 search similar term with treatment adherence including, self-care behaviors, physical activities and diet adher-
48 ence and so on.

49 **Our answer: Thank you for your comment. We sharpened the focus of the review accordingly and empha-**
50 **sized that the focus of the review is on medication adherence (but not the whole broader WHO definition)**
51 **(lines 64-65). A review on the associations between treatment adherence and health literacy as per the old**
52 **definition and the search terms mentioned by you would indeed be interesting.**
53
54

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

1
2
3
4 Lim, M. L., van Schooten, K. S., Radford, K. A., & Delbaere, K. (2020). Association between health literacy and
5 physical activity in older people: a systematic review and meta-analysis. *Health promotion international*,
6 daaa072. Advance online publication. <https://doi.org/10.1093/heapro/daaa072>
7
8 Cabellos-García, A. C., Martínez-Sabater, A., Castro-Sánchez, E., Kangasniemi, M., Juárez-Vela, R., & Gea-Cabal-
9 lero, V. (2018). Relation between health literacy, self-care and adherence to treatment with oral anticoagulants
10 in adults: a narrative systematic review. *BMC public health*, 18(1), 1157. [https://doi.org/10.1186/s12889-018-](https://doi.org/10.1186/s12889-018-6070-9)
11 6070-9

12 **Our answer: Thank you for this important comment and your literature recommendations. While we agree**
13 **with you, we did not include new search terms for treatment adherence since our aim was to examine medi-**
14 **cation adherence and health literacy, which we are optimistic we did. As explained above, we changed our**
15 **definition to medication adherence. (lines 64-65)**

16 **Thank you for your literature recommendations. Both show the need for further research on health literacy**
17 **and adherence in older adults as well as inclusion of different aspects of treatment adherence, which would**
18 **indeed be an interesting and important addition. Since we aimed to review the associations between health**
19 **literacy and medication adherence, we decided not to include further aspects of treatment adherence in our**
20 **review but will consider further research into these aspects.**

21
22
23 For method section, please explain why this review used only five databases. In case of medication adherence
24 as main component of treatment adherence, meaningful studies may be found in EMBASE. It is not familiar with
25 DB such as Epistemonikos, and LIVIVO

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

32
33
34 Regarding eligibility criteria, the authors presented treatment adherence by pill counts, questionnaires, screen-
35 ers, refill records. They only stand for measurement of medication adherence not overall type of treatment ad-
36 herence including behavior change, diet compliance and physical activities.

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

40
41
42 In table 1 and 2, the cells on the association between HL and TA are redundant.

43 **Our answer: Yes, you are correct. Thank you for this important comment. Of course, we deleted the redun-**
44 **dant cells in table 1. (line 235)**

45
46
47 Especially, it should be presented the confounding factors between HL and TA to provide new knowledge on
48 mechanism or pathway between HL and TA in older adults compared with previous systematic review in Table
49 3. In addition, please provide the cut off point or definition on HL such as inadequate and adequate H for stud-
50 ies in this review.

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

56
57
58 In discussion section, the authors addressed that TA in older adults is commonly assessed by proxy of MA,
59 which is measured with a wide range of tools. Vice versa, the authors should accurately define the range of TA
60 for achieving the goal of reviewing literatures.

1
2
3
4 **Our answer: Thank you. We agree this would be an important addition. However, since we aimed to review**
5 **medication adherence and health literacy in older adults, we did not directly add these aspects to our manu-**
6 **script. Nevertheless, we added further information resulting from other factors (e.g. physical activity) associ-**
7 **ated with health literacy and/or medication adherence to the discussion, again indicating the importance of**
8 **future research in this field (e.g. into physical activity and health literacy as mentioned by you). (lines 355-**
9 **372)**
10

11
12 For supplementary table on search strategies, the authors should present all search query based on each five
13 databases.

14 **Our answer: Thank you for your recommendation. We included all search strategies in the supplement.**
15

16 I hope these comments are helpful for improving quality of the paper.

17 **Our answer: Yes, we appreciate your time and expertise in reviewing our manuscript very much and hope we**
18 **were able to address all comments adequately to further improve the quality of our manuscript.**
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 "patient adherence"[All Fields]) OR ("adherence"[All Fields] OR "adhere"[All Fields] OR
4 "adhered"[All Fields] OR "adherence"[All Fields] OR "adherences"[All Fields] OR
5 "adherent"[All Fields] OR "adherents"[All Fields] OR "adherer"[All Fields] OR
6 "adherers"[All Fields] OR "adheres"[All Fields] OR "adhering"[All Fields]) OR "non-
7 adherence"[All Fields] OR ("nonadherence"[All Fields] OR "nonadherent"[All Fields] OR
8 "nonadherents"[All Fields] OR "nonadherers"[All Fields]) OR ("medication
9 adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR
10 "medication adherence"[All Fields]) OR ("discontinuance"[All Fields] OR
11 "discontinuances"[All Fields] OR "discontinued"[All Fields] OR "discontinuation"[All
12 Fields] OR "discontinuations"[All Fields] OR "discontinue"[All Fields] OR
13 "discontinued"[All Fields] OR "discontinuer"[All Fields] OR "discontinuers"[All Fields] OR
14 "discontinues"[All Fields] OR "discontinuing"[All Fields]) OR "non-compliance"[All Fields]
15 OR ("noncompliant"[All Fields] OR "noncompliers"[All Fields] OR "noncompliers"[All
16 Fields] OR "noncomplying"[All Fields] OR "patient compliance"[MeSH Terms] OR
17 ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields]
18 OR "noncompliance"[All Fields] OR "noncompliances"[All Fields]) OR ("terminal"[All
19 Fields] OR "terminal s"[All Fields] OR "terminally"[All Fields] OR "terminals"[All Fields]
20 OR "terminate"[All Fields] OR "terminated"[All Fields] OR "terminates"[All Fields] OR
21 "terminating"[All Fields] OR "termination"[All Fields] OR "terminations"[All Fields] OR
22 "terminator"[All Fields] OR "terminators"[All Fields]) OR ("refill"[All Fields] OR
23 "refillable"[All Fields] OR "refilled"[All Fields] OR "refilling"[All Fields] OR "refills"[All
24 Fields])) AND ("aged"[MeSH Terms] OR "aged"[All Fields] OR "old"[All Fields] OR
25 ("older"[All Fields] OR "olders"[All Fields]) OR ("aged"[MeSH Terms] OR "aged"[All
26 Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR
27 "elderlys"[All Fields]) OR ("geriatric"[All Fields] OR "geriatrics"[MeSH Terms] OR
28 "geriatrics"[All Fields]) OR "oldest"[All Fields] OR ("elder s"[All Fields] OR "elders"[All
29 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: ¹Total 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 <i>et al.</i> , 2013	BHLS 3 questions	<u>Range of overall HL scores:</u> 3-15 with higher scores indicating higher HL <u>Cutoff/ categories:</u> NA	MMAS-4	<u>Range of overall MA scores:</u> 0-4 with higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were dichotomized into nonadherence (scores ≤ 2) and adherence (scores ≥3)
Lee <i>et al.</i> , 2017	BHLS 15 questions	<u>Range of overall HL scores:</u> 15-75 with higher scores indicating higher HL <u>Cutoff/ categories:</u> NA	MMAS-8	<u>Range of overall MA scores:</u> 0-8 with higher scores indicating higher MA <u>Cutoff/ categories:</u> Scores were categorized into high (scores of 8), medium (scores 6-7), and low (scores ≤5) MA
Lu <i>et al.</i> , 2019	HLS-EU-Q16	<u>Range of overall HL scores:</u> 0-50 with higher scores indicating higher HL <u>Cutoff/ categories:</u> Scores ≤33 indicated limited HL, scores >34 indicated adequate HL	MOS-SAS	<u>Range of MA scores:</u> 0-5 with higher scores indicating higher MA <u>Cutoff/ categories:</u> Scores were dichotomized into adherence (scores ≥4) and nonadherence (scores ≤3)
Reading <i>et al.</i> , 2019	BHLS 3 questions	<u>Range of overall HL scores:</u> 3-15 with higher scores indicating higher HL <u>Cutoff/ categories:</u> HL was dichotomized into adequate and inadequate, but no cutoffs were reported	CARDIA (3 questions)	<u>Range of MA scores:</u> NA <u>Cutoff/ categories:</u> 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 <i>et al.</i> , 2019	SILS	<u>Range of overall HL scores:</u> 1-5 with higher scores indicating lower HL <u>Cutoff/ categories:</u> HL scores ≥3 indicated inadequate HL and scores ≤2 indicated adequate HL	MMAS-4	<u>Range of overall MA scores:</u> 0-4 with higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were dichotomized into nonadherence (scores ≤ 3) and adherence (scores of 4)
Seong <i>et al.</i> , 2019	BHLS 3 questions	<u>Range of overall HL scores:</u> 0-12 with higher scores indicating higher HL <u>Cutoff/ categories:</u> 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?")	<u>Range of overall MA scores:</u> 1-5 with higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were dichotomized into nonadherence (scores ≤ 5) and adherence (scores of 6)
Shehadeh-Sheeny <i>et al.</i> , 2013	FCCHL	<u>Range of overall HL scores:</u> NA, higher scores indicating higher HL <u>Cutoff/ categories:</u> HL scores were categorized into low, medium, and high HL, but no cut offs were reported/ are available	MPR	<u>Range of overall MA scores:</u> 0-1 (0%-100%), higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were categorized into low (MPR ≤ 0.2) and high (MPR ≥ 0.8) MA

1					
2					
3	Song & Park, 2020	BHLS 15 questions	<u>Range of overall HL scores:</u> 15-75 with higher scores indicating higher HL	MMAS-8	<u>Range of overall MA scores:</u> 0-8 with higher scores indicating higher MA
4					
5			<u>Cutoff/ categories:</u>		<u>Cutoff/ categories:</u>
6			NA		NA
7	Wannasirikul et al., 2016	FCCHL	<u>Range of overall HL scores:</u> 17-68 with higher scores indicating higher HL	ARMS	<u>Range of overall MA scores:</u> 14-56 with higher scores indicating higher MA
8					
9			<u>Cutoff/ categories:</u>		<u>Cutoff/ categories:</u>
10			HL scores were categorized into inadequate, marginal, and		NA
11			adequate HL, but no cut offs were reported/ are available		

12 **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
 13 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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3 **1 Self-reported health literacy and medication adherence in older adults: A systematic review**

4 2 Schönfeld MS¹, Pfisterer-Heise S², Bergelt C^{1,3}

5
6 3

7
8 ¹Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg,
9 Germany

10 ²Department of Biochemistry and Molecular Cell Biology, University Medical Centre Hamburg-
11 Eppendorf, Hamburg, Germany

12 ³Department of Medical Psychology, University Medicine Greifswald, Greifswald, Germany
13

14
15 **Corresponding author:**

16 **Moritz Sebastian Schönfeld**

17 University Medical Centre Hamburg-Eppendorf

18 Department of Medical Psychology

19 Martinistrasse 52

20 20246 Hamburg

21 Germany

22 mo.schoenfeld@uke.de

23 Tel: +49-40-7410-59140
24
25

26 4

27
28 **5 Word count**

29 6 5,463 words
30
31

32 **8 Date and version**

33 9 First submission of manuscript: October 29, 2020

34 10 1. Resubmission of revised manuscript: August 10, 2021

35 11 2. Resubmission of revised manuscript: August 26, 2021

36 12 3. Resubmission of revised manuscript: October 1, 2021
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 $\geq 66\%$ 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.

54 INTRODUCTION

55 Within the last decades, demographic change and increasing life expectancy have put older adults (≥ 60
56 years old as defined by the United Nations¹) in the focus of health care research. With increasing age, the
57 risk of chronic diseases and comorbidities rises resulting in a growing number of necessary treatments
58 (e.g. medication), and adherence to these treatments becomes crucial to reduce adverse reactions and
59 ensure safe and effective care. In this context, health literacy (HL), often defined as “the degree to which
60 individuals have the capacity to obtain, process, and understand basic health information and services
61 needed to make appropriate health decisions”², has been identified as a key influencing factor of
62 improving health-related behaviour in the elderly³. Accordingly, (elderly) people with low levels of HL use
63 health care more often and show higher rates of hospitalization than those with high levels of HL^{3,4}.

64 Research also confirmed low HL as a predictor of poor health outcomes linking lower HL to higher age⁵
65 ⁶, lower income⁵ and lower education^{3,7}. In addition, HL has been repeatedly linked to medication
66 adherence, commonly defined as “the extent to which a patient’s behaviour corresponds with the
67 prescribed medication dosing regime, including time, dosing and interval of medication intake”⁸.
68 Medication adherence (MA) has been the focus of this research since the number of medications taken
69 commonly increases with increasing age, making medication the most common form of therapy in the
70 elderly, often resulting in polypharmacy^{9,10}. Thus, MA still plays a crucial role in the elderly patient’s care.
71 However, research into the associations between HL and MA stays inconclusive¹¹⁻¹⁶. While multiple studies
72 report (significantly) positive associations between HL and MA¹⁷⁻²¹, others report (significantly) negative
73 associations^{22,23}.

74 Systematic reviews specifically conducted to analyse the relationship between HL and MA in the
75 elderly resulted in mixed findings as they often included studies with a variety of populations and measures
76 of HL^{12,16,24}. Older adults have commonly been examined as a homogenous group not taking into account
77 possible differences in levels of HL and MA between subgroups of age (e.g. 65-70 years old, 71-75 years
78 old, 76-80 years old, 85+ years old^{6,25}). In addition, reviews and meta-analyses examining the associations
79 between HL and MA in older age commonly included samples with a wide age range only focusing on the
80 mean age of samples. Since these samples often include (undisclosed) proportions of younger adults and
81 subgroups are not reported, results may not adequately reflect the relationship between HL and MA in
82 older adults^{24,26}. Previous reviews commonly aimed to include a wide selection of validated measures of
83 HL. However, since only a low proportion of relevant studies are measuring HL with self-reports, these
84 reviews often resulted in a focus on the so-called legacy instruments of HL (i.e. REALM²⁷, TOFHLA²⁸)^{12,24}
85 and thus included different measures and concepts of HL, which may have led to unknown bias^{15,26}. As
86 recently stated by Nguyen *et al.*²⁹, these often-deployed legacy tools may measure different aspects of
87 literacy and may not be appropriate to assess HL in older adults. Accordingly, limited HL was found to be
88 strongly associated with older age when measured with the TOFHLA (mainly assessing reading,
89 comprehension and numeracy skills²⁸) while limited HL had weak associations with older age³⁰ when
90 measured with the REALM (mainly assessing medical vocabulary²⁷).

91 As of late, these methodological shortcomings in research into HL have been increasingly recognized
92 leading to a broader discussion about the conceptualization and measurement of HL. Most recently,
93 researchers started concentrating on self-report measures of HL as new questionnaires from more
94 comprehensive concepts were developed (e.g. the HLS-EU-Q³¹). Compared to performance-based
95 measures, self-reports of HL commonly offer a fast, easy, and inexpensive way to collect data and have a
96 lower risk of stigma²⁹. Accordingly, self-reports present important advantages when assessing HL in

97 different populations and contexts as they can be applied more effortlessly. More recently, some studies
98 began to investigate levels of HL in different subgroups of older age resulting in a renewed call for more
99 differentiated methods and analyses in this population^{25 32}.

100 Thus, our review aims to systematically review the evidence on self-reported HL and MA in older adults
101 (≥ 60 years old) including: 1. the levels of self-reported HL and MA (if available, levels of different
102 subgroups); 2. the associations between self-reported HL and MA; 3. how self-reported HL and MA are
103 measured; and (if available) 4. moderator and mediator effects of other psychosocial factors.

104

105 **METHODS**

106 A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic
107 Reviews and Meta-Analyses (PRISMA) guidelines³³. A checklist of PRISMA items can be found in online
108 supplementary file S1. This review was registered with the International Prospective Register of Systematic
109 Reviews (PROSPERO): CRD42019141028. The protocol is presented in online supplementary file S2.

110

111 **Eligibility criteria**

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

115 **Intervention.** No specific interventions were included in the criteria. Nevertheless, only studies that
116 assessed associations (e.g. correlation, effect size) between self-reported HL and MA were deemed
117 eligible. Studies that assessed HL solely with a performance-based test instrument (e.g. REALM²⁷,
118 TOFHLA²⁸) were excluded from this review.

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

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

124

125 **Data sources and search strategy**

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

1
2
3 137 In addition, reference lists from eligible articles were hand searched accordingly. All references were
4 138 subsequently imported into Endnote X8 reference management software for screening purposes.
5
6 139

7 140 **Study selection and screening**

8 141 After removal of duplicates, two raters (MSS, SPH) screened titles and abstracts of all remaining studies
9 142 for eligibility. A checklist was developed for this purpose which included a list of inclusion and exclusion
10 143 criteria, such as type of measure of HL, MA, and included sample, to allow for a careful screening process.
11 144 As many studies include HL only as a secondary outcome and may thus not state it in the study's title or
12 145 abstract, a more liberal title/ abstract screening was conducted. Accordingly, two raters (MSS, SPH)
13 146 assessed the full texts of all previously screened studies independently. Figure 1 shows specific reasons for
14 147 study exclusion, which included lack of self-report HL measure, lack of MA measure, lack of associations
15 148 between HL and MA, lack of older adults in sample, lack of English or German language, being an ongoing
16 149 clinical trial with no results, lack of primary research (e.g. book chapter), lack of quantitative data (e.g.
17 150 interview study), or several of these reasons. In case of discrepancies, conflicts were discussed until
18 151 consensus was reached.
19
20
21
22 152

23 153 **Quality assessment**

24 154 The methodological quality of all studies included in this review was assessed using the NIH Quality
25 155 Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, NIH³⁴). Since only baseline
26 156 data from quantitative research was included, the NHLBI was deemed appropriate. The NHLBI contains 14
27 157 criteria mainly to assess the internal validity of a study. Each item was answered "yes" (if criterion was
28 158 met), "no" (if criterion was not met) or "cannot determine/ not applicable/ not reported". As the NHLBI is
29 159 not meant to assess the study quality by simply summing up its scores, an overall quality rating ("good",
30 160 "fair", "poor") for each study included a comprehensive and critical appraisal of each criterion as well as
31 161 the study as a whole.
32
33
34
35 162

36 163 **Data extraction and synthesis**

37 164 All relevant data was extracted by the first author with the help of a data extraction checklist that was
38 165 developed for this purpose and contained the following information about each included study: title,
39 166 authors, year published, study design and setting, sample and sample size, age subgroups, definition and
40 167 assessment of HL and MA, moderator and mediator effects (if available), statistical measures to calculate
41 168 associations between HL and MA (e.g. correlation), statistical significance if available.
42 169 As the studies showed heterogeneity due to differences in study design, participants, risk of bias, and
43 170 operationalization of HL and MA (e.g. different use of cutoffs and levels of HL), a narrative synthesis was
44 171 applied to analyse the studies thematically.
45
46
47
48 172

49 173 **Patient and public involvement**

50 174 Patients or the public were not involved in this study.
51
52
53 175

54 176 **RESULTS**

55 177
56
57
58
59
60

178 **Search results**

179 The literature search resulted in a total of 2,313 studies after removal of duplicates. After screening for
180 title and abstract another 1,769 studies were excluded based on exclusion criteria (figure 1). Full texts of
181 544 studies were screened and nine publications from eight studies met all eligibility criteria and were
182 thus included in this review (figure 1). The main reason for study exclusion in the screening process was
183 lack of self-reports of HL measure.

185 **Study characteristics**

186 Overall study characteristics are presented in table 1. All included publications were published between
187 2013 and 2020 with sample sizes between n=116 and n=12,159 (Median=293). The proportion of female
188 participants ranged from 33% to 100% (Median=53.6%). All studies adopted a cross-sectional design (5
189 survey studies). Three studies (four publications) were conducted in South Korea, and one study each in
190 China, USA, Pakistan, Israel, and Thailand. Studies were conducted across settings of tertiary care hospitals
191 (n=5), primary health care (n=1), private health care centres (n=1), community health care centres (n=1),
192 and clinics (n=1). All studies examined patients/adults with different types of (chronic) diseases:
193 hypertension (n=2), heart diseases (n=1), atrial fibrillation (n=2), osteoporosis (n=1), several chronic
194 diseases (n=3). Due to eligibility criteria restricting included samples to those with $\geq 66\%$ of older adults
195 (60 years of age and older), all studies focused on the elderly and only two studies also included patients
196 younger than 60 years (table 1). Five studies included samples with a higher proportion of women.

198 **Risk of bias**

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

203 **Health literacy – key findings**

204 In five publications from four studies³⁵⁻³⁹ self-reported HL was measured using a selection of questions
205 from the Brief Health Literacy Screen (BHLS⁴⁰). The BHLS employs three to fifteen questions (e.g. “How
206 often do you have someone help you read hospital materials?”) to identify people with inadequate levels
207 of HL. Another study⁴¹ used the short version of the European Health Literacy Survey Questionnaire (HLS-
208 EU-Q) which was designed by the HLS-EU-Consortium based on a conceptual framework of HL³¹. One study
209 assessed HL with the Single Item Literacy Screener (SILS), which asks ““How often do you need to have
210 someone help when you read instructions, pamphlets, or other written material from your doctor or
211 pharmacy?”⁴². Another two studies adopted the Functional, Communicative, and Critical Health Literacy
212 questionnaire (FCCHL) developed by Ishikawa *et al.*⁴³, a validated questionnaire that assesses three areas
213 of HL: functional HL, communicative HL, and critical HL.

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

1
2
3 221 Median=74.5%) whereas one study³⁷ found that a majority of the sample reported adequate levels of HL
4 222 (i.e. more people had high scores of HL; 76.9%).
5
6 223

7 224 **Medication adherence – key findings**

8 225 Four publications from three studies^{35 36 39 44} employed versions of the Morisky Medication Adherence
9 226 Scale (MMAS⁴⁷) to assess MA. The MMAS consists of four to eight questions asking about different aspects
10 227 of medication intake behaviour (e.g. “Do you sometimes forget to take your medication?”⁴⁷). One study⁴¹
11 228 used the Medical Outcomes Study Specific Adherence Scale (MOS-SAS⁴⁸) which addresses MA (“How often
12 229 have you done each of the following in the past 4 weeks: Took medication as prescribed (on time without
13 230 skipping dosis?)” as well as heart-healthy lifestyle behaviour (i.e. six preventive behaviours for coronary
14 231 heart disease, e.g. low-salt diet). One study³⁸ used a single-item adopted from Wu *et al.*⁴⁹ to assess MA
15 232 (“In the past week, have you forgotten to take your antithrombotic medication for various reasons?”).
16 233 Another study³⁷ adopted three questions from the Coronary Artery Risk Development in Young Adults
17 234 (CARDIA⁵⁰) to assess MA (1. “In the past month, how often did you take your medications as the doctor
18 235 prescribed?”; 2. “In the past month, how often did you forget to take 1 or more of your prescribed
19 236 medications?”; 3. “In the past month, how often did you decide to skip 1 or more of your prescribed
20 237 medications?”). MA was also assessed by the Medication Possession Ratio (MPR) in one study⁴⁵. The MPR
21 238 commonly represents the period during which a patient has an adequate amount of supply of his/her
22 239 medication available over a predefined amount of time (e.g. a year). One study assessed MA with the
23 240 Adherence to Refills and Medication Scale (ARMS⁵¹) which assesses if a patient can correctly take and refill
24 241 his or her medication on schedule.

25 242 Overall, five publications from four studies^{35 36 38 44 45} found that a majority of the sample reported low
26 243 levels of MA (i.e. more non-adherers; range from 50.2% to 69.4%, Median=59.0%) while three studies^{37 41}
27 244 ⁴⁶ in contrast, found that a majority of the sample reported high levels of MA (i.e. more adherers; range
28 245 from 84.7% to 98.3%, Median=93.7%). One study reported a sample mean score of MA only³⁹.

Table 1. Overall summary of included studies

Authors, year	Setting, country	Sample				Disease	Risk of bias ¹
		N	Age (years), mean (±SD)	% Female	Age subgroups		
Lee <i>et al.</i> , 2013 ³⁵	Tertiary care hospitals, South Korea	n=293	65+ M=74.4 (6.3)	46.8%	NA	Chronic Diseases	fair
Lee <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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, NIH³⁴). NA: Not available/ not reported.

248 Age subgroups – key findings

249 Seven studies^{36-39 41 44 45} included in this review examined age subgroups for differences in HL and/or MA.
 250 All of these studies conducted subgroup analyses for differences in MA while only one of these studies⁴¹
 251 examined differences in HL between age subgroups (e.g. 65-75 years old, 76-85 years old, >85 years old;
 252 table 2).

253 Overall, four studies^{36 41 44 45} found no significant differences in MA between age subgroups while one
 254 study³⁷ reported age as a significant predictor of medication nonadherence as younger patients (<65 years
 255 old) were more likely to be nonadherent compared to old/older patients (age groups 65-74 years old and
 256 75-84 years old) but not compared to the oldest (≥85 years old). One study³⁹ reported higher MA in 65-69-
 257 year-old adults compared to 70-79-year-old adults and ≥80-year-old adults. Another study³⁸ reported
 258 significant differences in adherence levels between age subgroups but did not confirm age as a significant
 259 predictor of medication nonadherence in multivariate analyses. Age was significantly associated with HL
 260 in one study⁴¹ as patients with limited HL were significantly older compared to those with adequate HL.
 261 However, regression analyses did not confirm age as a predictor of limited HL (table 2).
 262

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 <i>et al.</i> , 2013 ³⁵	NA	None conducted
Lee <i>et al.</i> , 2017 ³⁶	65-74 (57.0%) ≥75 (43.0%)	No significant differences in MA between age groups ($\chi^2=0.391$, $p=0.835$)
Lu <i>et al.</i> , 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 <ul style="list-style-type: none"> - 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 <ul style="list-style-type: none"> - 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 <i>et al.</i> , 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 <ul style="list-style-type: none"> - 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 <ul style="list-style-type: none"> - patients ≥85 years old (AOR (95% CI) = 0.86 (0.64-1.16), n.s.)
Saqlain <i>et</i>	65-75 (84.7%)	No significant differences in MA between age groups ($\chi^2=1.631$, $p=0.442$)

<i>al.</i> , 2019 ⁴⁴	76-85 (11.1%) >85 (4.2%)	
Seong <i>et al.</i> , 2019 ³⁸	65-70 (32.1%) 70-79 (45.5%) ≥80 (22.4%)	Adherence to medication significantly differed with respect to age ($\chi^2=15.15$, $p<0.001$) 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 <i>et al.</i> , 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 <i>et al.</i> , 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 study³⁸ reported mixed findings. In detail, one of two publications³⁵ from one study confirmed HL as the strongest predictor for MA in a hierarchical regression analysis while another publication³⁵ 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 study⁴¹ 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 fibrillation³⁷, 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 hypertension⁴⁴ found positive and statistically

1
2
3 285 significant associations between HL and MA as well as a higher likelihood of patients with adequate levels
4 286 of HL to be adherent to medication compared to patients with inadequate levels of HL. In their multivariate
5 287 logistic regression, the same study found that in addition to adequate HL, self-reported good and
6 288 moderate subjective health as well as independence in activities of daily living were also independent
7 289 predictors of MA in the elderly. Another study³⁸ reported significant differences in adherence to
8 290 antithrombotic medication by levels of HL but did not confirm HL as a significant predictor for MA in older
9 291 adults. They concluded that a significant association between HL and MA might exist still since in their
10 292 univariate regression the rate of inadequate HL was higher in the group of nonadherent patients compared
11 293 to adherent patients. However, in their multivariate logistic regression, the authors³⁸ found only cognitive
12 294 impairment to be a significant predictor of medication nonadherence in older patients with atrial
13 295 fibrillation. One study⁴⁵ found no significant association between HL and MA in a population of female
14 296 osteoporosis patients and found only self-reported income to be a significant predictor of adherence in
15 297 the conducted multivariate logistic regression. Another study³⁹ found significantly positive associations
16 298 between HL and MA. In their multiple regression analysis, the authors also found that income, number of
17 299 chronic diseases, vision problems, and HL were significant predictors of MA. One other study⁴⁶ analysed
18 300 the relationship between HL, MA, and blood pressure levels in primary care patients with hypertension
19 301 using a Structural Equation Modeling (SEM) approach, which supported the existence of a causal
20 302 relationship between these factors. Accordingly, HL had a positive but small statistically significant direct
21 303 effect on MA. Literacy and cognitive ability had the biggest direct effects on both HL and MA. Additionally,
22 304 HL had the biggest significantly negative direct effect on blood pressure levels (i.e. the higher the HL, the
23 305 lower the blood pressure level). Based on the SEM, the authors of this study⁴⁶ suggested a mediator effect
24 306 of HL on MA, even though no analysis was conducted. None of the other studies performed mediator
25 307 and/or moderator analyses concerning HL and/or MA and other factors

1
2
3 308
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

For peer review only

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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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)

1						
2						
3	Saqlain <i>et al.</i> , 2019 ⁴⁴	n=262, 65+ years	SILS	MMAS-4	n=98 (37.4%) patients had adequate HL	Positive and statistically significant associations between HL and MA ($\chi^2=24.356$, $p<0.001$)
4						
5		M=NA			n=102 (38.9%) patients were adherent to medication	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), $p<0.001$)
6						
7		Outpatients with				
8		hypertension from tertiary				
9		health care centres in				
10		Islamabad, Pakistan				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), $p<0.002$)
11	Seong <i>et al.</i> , 2019 ³⁸	n=277, 65+ years	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	Positive and statistically significant associations between HL and MA ($\chi^2=22.00$, $p<0.001$)
12						
13		M=74.2 (7.2)				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), $p=0.002$)
14		Outpatients with atrial				
15		fibrillation undergoing				
16		antithrombotic therapy in				
17		tertiary general hospital in				
18		South Korea			n=139 (50.2%) patients were nonadherent to medication	
19					Significant differences in MA between age subgroups ($p<0.001$)	
20	Shehadeh- Sheeny <i>et al.</i> , 2013 ⁴⁵	n=303, 60+ years	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	No significant associations between MA and HL ($p=0.44$)
21						
22		M= 71 (6.04)				46.7% of patients with high HL were more adherent to medication compared to 35.9% of patients with low HL
23						
24		Female Arab patients				
25		with osteoporosis				
26		from three clinics in Israel			n=125 (41.3%) patients had high MA	In multivariate logistic regression only self-reported income was a significant predictor of MA (OR (95% CI) = 1.26 (1.01-1.58), $p=0.037$)
27	Song & Park, 2020 ³⁹	n=116, 65+ years	BHLS 15 questions	MMAS-8	Mean HL was 42.4 (6.6)	HL positively correlated with MA ($r=0.42$, $p<0.001$)
28						
29		M=72.7 (6.1)				In multiple regression analysis HL was significant predictor of MA ($\beta=0.23$, $p<0.001$)
30		Community-dwelling older			Mean MA was at a medium level (M=4.3 (2.2))	Other significant predictors of MA were income ($\beta=0.35$, $p<0.001$), number of chronic diseases ($\beta=-0.33$, $p<0.001$), and vision problems ($\beta=-0.32$, $p<0.001$)
31		adults in health care				
32		centre, South Korea				
33						
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Wannasirikul <i>et al.</i> , 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 ($\beta=0.08$, $p<0.05$) Cognitive ability ($\beta=0.22$, $p<0.05$) and literacy ($\beta=0.46$, $p<0.05$) had biggest and significantly positive direct effect on MA Literacy ($\beta=0.15$, $p<0.05$) and cognitive ability ($\beta=0.52$, $p<0.05$) had biggest and significantly positive direct effect on HL HL had biggest significantly negative direct effect on blood pressure level ($\beta=-0.14$, $p<0.05$) MA had a significantly negative direct effect on blood pressure level ($\beta=-0.02$, $p<0.05$) Results suggest mediator effect of HL on MA
--	--	-------	------	--	--

309 **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
310 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.

311 DISCUSSION

312 The aim of this study was to give a systematic overview of the associations between HL and MA in older
313 adults. Although research on HL and MA in older adults has rapidly increased in the last years, mixed results
314 are a common denominator in this area^{15 52}. Accordingly, previous systematic reviews resulted in a range
315 of conclusions as they included a variety of HL concepts, different (younger) age groups, and a range of
316 methodologically different instruments (self-reports as well as performance-based measures) to assess
317 HL^{12 16 24 26 52}. To our knowledge, this is the first systematic review to focus specifically on self-reported HL
318 while explicitly including studies with samples of older adults. We found that only few validated
319 instruments of self-reported HL are used and that most studies still rely on legacy measures to assess HL
320 even though their use has been criticized repeatedly and self-reports of HL offer a range of advantages²⁹.
321 Studies included in our review mostly assessed MA in older adults through self-reports, even though a
322 wide range of tools is known^{53 54}.

323 In this review, results appear to be more consistent in contrast to previous reviews^{15 16} as many
324 included studies reported positive and statistically significant associations between HL and MA. This could
325 be explained by the fact that only older adults (at least 66% of older adults in samples, not based on the
326 samples' mean age) were examined in the included studies and associations in this group may be more
327 prominent compared to studies that also include subgroups of younger people. One review²⁴ for example
328 aimed to review literature that examined HL and MA in older adults with cardiovascular disease or
329 diabetes. Included studies in the review had to assess HL with legacy instruments only and had to include
330 samples of participants with a "[...] mean age [of] at least 50 years or with at least a third of participants
331 aged 50 years or older [...]" and could not confirm an association between HL and MA. As stated earlier,
332 inclusion of younger participants may have resulted in unknown bias from age. Yet another bias may have
333 resulted from the utilization of legacy measures with different conceptualizations of HL since the REALM
334 and TOFHLA, two of the most prominent legacy tools of HL, are confirmed to assess different aspects of
335 literacy rather than HL and may thus be differently impacted by a person's intelligence²⁹. Accordingly, Loke
336 *et al.* stated in their review that functional measures of HL may not be adequate and "[n]ew methods of
337 measuring health literacy beyond the functional level are needed [...]".

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

1
2
3 354 reported HL are still widely lacking, we need more research to explore and develop comprehensive
4 355 theories in this area.

5 356 Six studies^{37 38 41 44-46} included in this review found that a majority of participants in the respective
6 357 samples reported limited (i.e. inadequate, low, marginal) HL. This is consistent with other research that
7 358 showed that older people commonly reach only low levels of self-reported health literacy^{3 25 32} even though
8 359 this research is very scarce. HL was measured by versions of four different self-reports (BHLS^{40 55}, HLS-EU-
9 360 Q³, SILS⁴², FCCHL⁴³). This shows that self-reporting HL measures are still rarely utilized when examining
10 361 older adults, even though the Health literacy Tool Shed⁵⁶ lists 29 self-report instruments for HL in English
11 362 alone (58 without language restrictions).

12 363 MA was assessed through self-reports in all but one of the included studies^{35-39 41 44 46}. Nevertheless,
13 364 we recommend a more detailed description of operationalization of MA as many studies still use the
14 365 concepts of adherence and compliance interchangeably. Interestingly, we had to exclude many studies
15 366 from this review even though they assessed some form of adherence, because they only included
16 367 measures of general preventive behaviour (e.g. physical activity) and not MA. However, the use of such
17 368 secondary adherence measures might be a promising approach to get a more comprehensive picture of
18 369 adherence in older adults⁵⁴. Especially a multi-method approach could be helpful since self-reported
19 370 adherence may also be affected by cognitive bias and/or social desirability in older adults. As such, the
20 371 utilization of both direct (e.g. laboratory measures) and indirect (e.g. self-reports) measures of
21 372 adherence^{54 57} may help to get a better understanding of adherence and its associations with self-reported
22 373 HL in older adults. A number of studies in this review also included measures of secondary prevention (e.g.
23 374 physical activity, heart-healthy lifestyle behavior) as well as other factors (e.g. income, cognitive ability)
24 375 providing further knowledge on possible confounders in the mechanisms between HL and MA.
25 376 Accordingly, several studies confirmed multiple other factors as predictors for MA (e.g., health status^{36 37}
26 377 ⁴⁴, income^{39 45}, physical activity^{37 44}, cognitive ability^{38 46}) and/ or HL (e.g., cognitive ability⁴⁶, stress
27 378 management⁴¹). In a recent systematic review and meta-analysis by Lim et al.⁵⁸, the authors examined the
28 379 associations between physical activity and HL and found that older adults with inadequate levels of HL
29 380 were “[...] less likely [...] to report engaging in physical activity [...]” than those with adequate HL, showing
30 381 the importance of also addressing secondary adherence measures in future research in this area. Notably,
31 382 their review also included younger adults (samples with mean age ≥55 years) and different of HL measures
32 383 (legacy measures and self-reports).

33 384 Even though we also encourage researchers to assess HL with a multi-method approach (e.g.
34 385 subjective and objective instruments), we suggest a more rigorous differentiation in analysis and
35 386 interpretation when comparing HL measures that are based on different concepts (e.g. legacy tools and
36 387 self-reports). This may also help to clarify further the associations between self-reported HL and literacy
37 388 as measured by legacy instruments. As stated by Nguyen *et al.*²⁹, a separation in analyses of objective and
38 389 subjective measures of HL as well as a closer alignment of HL theory and measurement could help clarify
39 390 the relationship between HL and MA. This idea was also supported by one of the studies³⁹ included in this
40 391 review, which aimed at comparing two different measures of HL (self-report vs. legacy measure). The
41 392 authors found that even though both measures were significantly and positively correlated to MA, only
42 393 the self-report was a significant predictor for MA in older adults suggesting that self-reports may be more
43 394 fitting to assess HL when predicting MA since “[...] assessing older adults’ experiences of limited health
44 395 literacy is more appropriate for catching any decreased medication adherence [...]”.

1
2
3 396 This review additionally confirms that age subgroup analyses are conducted very rarely for self-
4 397 reported HL but quite often for MA. This may result from the fact that research on MA in the elderly is
5 398 traditionally older than research on HL in the elderly and with regard to HL most studies still treat older
6 399 people as a homogenous group²⁵. Most studies in this review did not find any significant associations
7 400 between age and MA and only two studies^{37 39} reported significant differences in MA between age
8 401 subgroups. Accordingly, one study³⁷ reported that young/ young-old people (21-65 years old) were more
9 402 likely not to adhere to their medication compared to old/older adults (65-84 years old) but not oldest
10 403 adults (≥ 85 years old). A second study³⁹ reported higher MA in 65-69-year-old adults compared to
11 404 older/oldest adults (70-90 years old). Not surprisingly, only one study conducted analyses on the
12 405 relationship between age and HL⁴¹, showing that patients with limited HL were significantly older
13 406 compared to those with adequate HL. Even though generalizability is very limited, these results reveal the
14 407 necessity for more differentiated analyses (e.g. of subgroups) in future HL and MA research on older
15 408 adults. In context of demographic change and increasing life expectancy, more differentiated analyses
16 409 could help to understand specific needs and barriers of elderly (patient) populations with different chronic
17 410 diseases. Importantly, definitions of *old age* are often inconsistent and include people from ages 60, 65,
18 411 or 70 years and over. These dissimilarities in the definitions of old age may result from differences in
19 412 cultural and/or economic standards (e.g. USA vs. Asia) and often manifest in different demographic
20 413 changes and/or different life expectancies thus resulting in a different quality of health care in groups of
21 414 older adults. Consequently, when looking at older adults' health care and health outcomes, it is critical to
22 415 include contextual aspects such as cultural or economic standards.

23 416 Studies in this review show some inconsistencies in the use of cutoffs, use, and wording of HL levels.
24 417 Of all included studies, six studies^{37 38 41 44-46} reported categories of HL (e.g. adequate) of which only three³⁸
25 418 ^{41 44} reported cutoffs for these categories. Three publications^{35 36 39} from two studies reported neither
26 419 categories nor cutoffs for HL and only five publications^{35 36 38 39 46} from four studies reported mean values
27 420 of HL. For example, Shehadeh-Sheeny et al. calculated scores for low, medium, and high levels of HL while
28 421 Wannasirikul et al. calculated scores for adequate, marginal, and inadequate HL levels even though no
29 422 cutoffs were reported/available by neither the authors nor the FCCHL measure both studies used. The
30 423 inconsistent use of cutoffs and wording may indicate a lack of certainty and experience in the application
31 424 of self-reports enhancing the call for more differentiated research and the development of easy-to-use
32 425 but still valid tools.

33 426
34
35
36
37
38
39
40
41
42
43
44
45 427 **Strength and limitations**
46 428 The strengths of this study include the exhaustive methodology and comprehensive search strategy that
47 429 were used. As we followed a strict screening procedure, we are confident that we found all eligible studies.
48 430 Since we excluded all studies that measured HL with performance-based instruments, we aimed to reduce
49 431 bias resulting from fundamental differences in constructs and concepts. Although we see this exclusion as
50 432 a considerable advantage, we cannot eliminate the possibility of bias still resulting from theoretical or
51 433 practical differences in self-reports as some of them are built on more complex conceptual frameworks
52 434 than others. Additionally, there are advantages in assessing HL in older adults with self-reports since they
53 435 reduce the possible bias of performance-based measures resulting from fear of stigma and/or (time)

1
2
3 436 pressure. Nevertheless, we recognize the inherent limitations of self-reporting tools that may also have
4 437 biased our results.

5 438 Other limitations should be considered. All studies included in this review were cross-sectional, thus
6 439 we cannot determine any direction of causality. The fair to poor methodological quality of the included
7 440 studies may also increase the risk of (unknown) bias. Given the heterogeneity of the studies, a meta-
8 441 analysis (e.g. pooled odds ratios) could not be conducted, thus limiting further understanding of the
9 442 relationship between HL and MA in older adults. Additionally, our search strategy in this review limited
10 443 included studies to English and German, which could bias results due to missing research in other
11 444 languages. Finally, we were not able to include EMBASE as a database in our search. Even though, we are
12 445 very confident that we did not miss a substantial amount of literature, this must be considered as a
13 446 limitation of this review.

14
15
16
17
18
19 447

20 21 448 **CONCLUSIONS**

22 449 In this review, self-reported HL and MA in older adults show a rather straightforward positive association.
23 450 While previous research on HL and MA in older adults did not always find clear associations, many studies
24 451 included in this review reported significantly positive associations between HL and MA. In addition, HL
25 452 plays an important role as a predictor of MA in older adults as several studies in this review could confirm.
26 453 However, other factors (e.g. cognitive ability) appear equally important in predicting MA in older adults,
27 454 and future studies should also focus on secondary adherence measures (e.g. physical activity) when
28 455 examining the associations between HL and MA in the elderly. Finally, study heterogeneity and
29 456 methodological weaknesses reveal a definitive need for more differentiated research regarding different
30 457 definitions, concepts, and measures of HL and MA as well as longitudinal research designs and studies that
31 458 analyse age subgroups in older adults.

1
2
3 459 **Acknowledgements**

4 460 We would like to thank Dr. rer. biol. hum. Laura Inhestern for her advice during the preparation of the
5 461 search for this review.
6 462

7 463 **Author Contributions**

8 464 All authors were involved in the design and planning of the review. MSS prepared, performed, and
9 465 redefined the searches after consultation with SPH and CB. MSS and SPH performed screening and data
10 466 extraction with the help of CB in case of disagreements or discussion. All authors contributed to the data
11 467 analysis and interpretation. MSS wrote the first draft which was critically revised by SPH and CB.
12 468

13 469 **Ethics Approval Statement**

14 470 This study does not involve human participants, as it is a systematic review.
15 471

16 472 **Funding**

17 473 This research received no specific grant from any funding agency in the public, commercial or not-for-
18 474 profit sectors.
19 475

20 476 **Competing interests**

21 477 None declared.
22 478

23 479 **Patient consent**

24 480 Not required.
25 481

26 482 **Provenance and peer review**

27 483 Not commissioned; externally peer reviewed.
28 484

29 485 **Data sharing statement**

30 486 All data relevant to the study are included in the article or uploaded as supplementary information.
31 487

32 488 **Open Access**

33 489 This is an open access article distributed in accordance with the Creative Commons Attribution Non
34 490 Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work
35 491 non-commercially, and license their derivative works on different terms, provided the original work is
36 492 properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial.
37 See: <http://creativecommons.org/licenses/by-nc/4.0/>.

493 REFERENCES

- 494 1 United Nations, Department of Economic and Social Affairs, Population Division. World Population
495 Ageing 2019: Highlights (ST/ESA/SER.A/430). 2019.
- 496 2 Ratzan SC, Parker RM. Health literacy - identification and response. *J Health Commun* 2006;**11**:713-
497 5.doi:10.1080/10810730601031090
- 498 3 Consortium H-E. Comparative Report on Health Literacy in Eight EU Member States. The European
499 Health Literacy Project 2009–2012. Vienna: Ludwig Boltzmann Institute for Health Promotion Research
500 2012.
- 501 4 Berkman ND, Sheridan SL, Donahue KE, et al. Low health literacy and health outcomes: an updated
502 systematic review. *Ann Intern Med* 2011;**155**:97-107.doi:10.7326/0003-4819-155-2-201107190-00005
- 503 5 Chesser AK, Keene Woods N, Smothers K, et al. Health Literacy and Older Adults: A Systematic Review.
504 *Gerontol Geriatr Med* 2016;**2**:2333721416630492.doi:10.1177/2333721416630492
- 505 6 Vogt D, Schaeffer D, Messer M, et al. Health literacy in old age: results of a German cross-sectional
506 study. *Health Promot Int* 2018;**33**:739-47.doi:10.1093/heapro/dax012
- 507 7 Wolf MS, Feinglass J, Thompson J, et al. In search of 'low health literacy': threshold vs. gradient effect
508 of literacy on health status and mortality. *Soc Sci Med* 2010;**70**:1335-
509 41.doi:10.1016/j.socscimed.2009.12.013
- 510 8 Gast A, Mathes T. Medication adherence influencing factors—an (updated) overview of systematic
511 reviews. *Systematic Reviews* 2019;**8**:1-17.doi:10.1186/s13643-019-1014-8
- 512 9 Hoel RW, Giddings Connolly RM, Takahashi PY. Polypharmacy Management in Older Patients. *Mayo*
513 *Clinic Proceedings* 2021;**96**:242-56.doi:10.1016/j.mayocp.2020.06.012
- 514 10 Chiatti C, Bustacchini S, Furneri G, et al. The economic burden of inappropriate drug prescribing, lack
515 of adherence and compliance, adverse drug events in older people: a systematic review. *Drug Saf*
516 2012;**35 Suppl 1**:73-87.doi:10.1007/BF03319105
- 517 11 Huang YM, Shiyabola OO, Smith PD. Association of health literacy and medication self-efficacy with
518 medication adherence and diabetes control. *Patient Prefer Adherence* 2018;**12**:793-
519 802.doi:10.2147/PPA.S153312
- 520 12 Martins NFF, Abreu DPG, Silva BTD, et al. Functional health literacy and adherence to the medication
521 in older adults: integrative review. *Rev Bras Enferm* 2017;**70**:868-74.doi:10.1590/0034-7167-2016-0625
- 522 13 Park NH, Song MS, Shin SY, et al. The effects of medication adherence and health literacy on health-
523 related quality of life in older people with hypertension. *Int J Older People Nurs*
524 2018;**13**:e12196.doi:10.1111/opn.12196
- 525 14 Roh YH, Koh YD, Noh JH, et al. Effect of health literacy on adherence to osteoporosis treatment
526 among patients with distal radius fracture. *Arch Osteoporos* 2017;**12**:42.doi:10.1007/s11657-017-0337-0
- 527 15 Zhang NJ, Terry A, McHorney CA. Impact of health literacy on medication adherence: a systematic
528 review and meta-analysis. *Ann Pharmacother* 2014;**48**:741-51.doi:10.1177/1060028014526562
- 529 16 Ostini R, Kairuz T. Investigating the association between health literacy and non-adherence.
530 *International journal of clinical pharmacy* 2014;**36**:36-44.doi:10.1007/s11096-013-9895-4
- 531 17 Lindquist LA, Go L, Fleisher J, et al. Relationship of health literacy to intentional and unintentional
532 non-adherence of hospital discharge medications. *J Gen Intern Med* 2012;**27**:173-8.doi:10.1007/s11606-
533 011-1886-3
- 534 18 Wolf MS, Davis TC, Osborn CY, et al. Literacy, self-efficacy, and HIV medication adherence. *Patient*
535 *Educ Couns* 2007;**65**:253-60.doi:10.1016/j.pec.2006.08.006
- 536 19 Kripalani S, Gatti ME, Jacobson TA. Association of age, health literacy, and medication management
537 strategies with cardiovascular medication adherence. *Patient Educ Couns* 2010;**81**:177-
538 81.doi:10.1016/j.pec.2010.04.030
- 539 20 Bauer AM, Schillinger D, Parker MM, et al. Health literacy and antidepressant medication adherence
540 among adults with diabetes: the diabetes study of Northern California (DISTANCE). *J Gen Intern Med*
541 2013;**28**:1181-7.doi:10.1007/s11606-013-2402-8

- 1
2
3 542 21 Mayo-Gamble TL, Mouton C. Examining the Association Between Health Literacy and Medication
4 543 Adherence Among Older Adults. *Health Commun* 2018;**33**:1124-30.doi:10.1080/10410236.2017.1331311
5 544 22 Mosher HJ, Lund BC, Kripalani S, et al. Association of health literacy with medication knowledge,
6 545 adherence, and adverse drug events among elderly veterans. *J Health Commun* 2012;**17 Suppl 3**:241-
7 546 51.doi:10.1080/10810730.2012.712611
8 547 23 Fang MC, Machtinger EL, Wang F, et al. Health literacy and anticoagulation-related outcomes among
9 548 patients taking warfarin. *J Gen Intern Med* 2006;**21**:841-6.doi:10.1111/j.1525-1497.2006.00537.x
10 549 24 Loke YK, Hinz I, Wang X, et al. Systematic review of consistency between adherence to cardiovascular
11 550 or diabetes medication and health literacy in older adults. *Ann Pharmacother* 2012;**46**:863-
12 551 72.doi:10.1345/aph.1Q718
13 552 25 Vogt D, Berens EM, Schaeffer D. Gesundheitskompetenz im höheren Lebensalter [Health Literacy in
14 553 Advanced Age]. *Gesundheitswesen* 2020;**82**:407-12.doi:10.1055/a-0667-8382
15 554 26 Geboers B, Brainard JS, Loke YK, et al. The association of health literacy with adherence in older
16 555 adults, and its role in interventions: a systematic meta-review. *BMC Public Health*
17 556 2015;**15**:903.doi:10.1186/s12889-015-2251-y
18 557 27 Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened
19 558 screening instrument. *Fam Med* 1993;**25**:391-5
20 559 28 Parker RM, Baker DW, Williams MV, et al. The test of functional health literacy in adults: a new
21 560 instrument for measuring patients' literacy skills. *J Gen Intern Med* 1995;**10**:537-
22 561 41.doi:10.1007/BF02640361
23 562 29 Nguyen TH, Paasche-Orlow MK, McCormack LA. The state of the science of health literacy
24 563 measurement. *Information Services & Use* 2017;**37**:189-203.doi:10.3233/ISU-170827
25 564 30 Kobayashi LC, Wardle J, Wolf MS, et al. Aging and Functional Health Literacy: A Systematic Review
26 565 and Meta-Analysis. *J Gerontol B Psychol Sci Soc Sci* 2016;**71**:445-57.doi:10.1093/geronb/gbu161
27 566 31 Sørensen K, Van den Broucke S, Pelikan JM, et al. Measuring health literacy in populations:
28 567 illuminating the design and development process of the European Health Literacy Survey Questionnaire
29 568 (HLS-EU-Q). *BMC Public Health* 2013;**13**:948.doi:10.1186/1471-2458-13-948
30 569 32 Berens EM, Vogt D, Messer M, et al. Health literacy among different age groups in Germany: results
31 570 of a cross-sectional survey. *BMC Public Health* 2016;**16**:1151.doi:10.1186/s12889-016-3810-6
32 571 33 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-
33 572 analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.doi:10.1371/journal.pmed.1000097
34 573 34 National Heart, Lung, and Blood Institute.. Quality Assessment Tool for Observational Cohort and
35 574 Cross-Sectional Studies, 2014. Available: [https://www.nhlbi.nih.gov/health-pro/guidelines/in-](https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort)
36 575 [develop/cardiovascular-risk-reduction/tools/cohort](https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort) [Accessed 05 May 2020].
37 576 35 Lee SK, Kang BY, Kim HG, et al. Predictors of medication adherence in elderly patients with chronic
38 577 diseases using support vector machine models. *Healthc Inform Res* 2013;**19**:33-
39 578 41.doi:10.4258/hir.2013.19.1.33
40 579 36 Lee YM, Yu HY, You MA, et al. Impact of health literacy on medication adherence in older people with
41 580 chronic diseases. *Collegian* 2017;**24**:11-8.doi:10.1016/j.colegn.2015.08.003
42 581 37 Reading SR, Black MH, Singer DE, et al. Risk factors for medication non-adherence among atrial
43 582 fibrillation patients. *BMC Cardiovasc Disord* 2019;**19**:38.doi:10.1186/s12872-019-1019-1
44 583 38 Seong HJ, Lee K, Kim BH, et al. Cognitive Impairment Is Independently Associated with Non-
45 584 Adherence to Antithrombotic Therapy in Older Patients with Atrial Fibrillation. *Int J Environ Res Public*
46 585 *Health* 2019;**16**.doi:10.3390/ijerph16152698
47 586 39 Song MS, Park S. Comparing two health literacy measurements used for assessing older adults'
48 587 medication adherence. *J Clin Nurs* 2020;**29**:4313-20.doi:10.1111/jocn.15468
49 588 40 Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy.
50 589 *Fam Med* 2004;**36**:588-94

- 1
2
3 590 41 Lu M, Ma J, Lin Y, et al. Relationship between patient's health literacy and adherence to coronary
4 591 heart disease secondary prevention measures. *J Clin Nurs* 2019;**28**:2833-43.doi:10.1111/jocn.14865
5 592 42 Morris NS, MacLean CD, Chew LD, et al. The Single Item Literacy Screener: evaluation of a brief
6 593 instrument to identify limited reading ability. *BMC Fam Pract* 2006;**7**:21.doi:10.1186/1471-2296-7-21
7 594 43 Ishikawa H, Takeuchi T, Yano E. Measuring functional, communicative, and critical health literacy
8 595 among diabetic patients. *Diabetes Care* 2008;**31**:874-9.doi:10.2337/dc07-1932
9 596 44 Saqlain M, Riaz A, Malik MN, et al. Medication Adherence and Its Association with Health Literacy
10 597 and Performance in Activities of Daily Livings among Elderly Hypertensive Patients in Islamabad,
11 598 Pakistan. *Medicina (Kaunas)* 2019;**55**.doi:10.3390/medicina55050163
12 599 45 Shehadeh-Sheeny A, Eilat-Tsanani S, Bishara E, et al. Knowledge and health literacy are not
13 600 associated with osteoporotic medication adherence, however income is, in Arab postmenopausal
14 601 women. *Patient Educ Couns* 2013;**93**:282-8.doi:10.1016/j.pec.2013.06.014
15 602 46 Wannasirikul P, Termsirikulchai L, Sujirarat D, et al. Health Literacy, Medication Adherence, and
16 603 Blood Pressure Level among Hypertensive Older Adults Treated at Primary Health Care Centers.
17 604 *Southeast Asian J Trop Med Public Health* 2016;**47**:109-20
18 605 47 Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of
19 606 medication adherence. *Med Care* 1986;**24**:67-74.doi:10.1097/00005650-198601000-00007
20 607 48 Sherbourne CD, Hays RD, Ordway L, et al. Antecedents of adherence to medical recommendations:
21 608 results from the Medical Outcomes Study. *J Behav Med* 1992;**15**:447-68.doi:10.1007/BF00844941
22 609 49 Wu JR, DeWalt DA, Baker DW, et al. A single-item self-report medication adherence question predicts
23 610 hospitalisation and death in patients with heart failure. *J Clin Nurs* 2014;**23**:2554-
24 611 64.doi:10.1111/jocn.12471
25 612 50 Cutter GR, Burke GL, Dyer AR, et al. Cardiovascular risk factors in young adults. The CARDIA baseline
26 613 monograph. *Control Clin Trials* 1991;**12**:1S-77S.doi:10.1016/0197-2456(91)90002-4
27 614 51 Kripalani S, Risser J, Gatti ME, et al. Development and evaluation of the Adherence to Refills and
28 615 Medications Scale (ARMS) among low-literacy patients with chronic disease. *Value Health* 2009;**12**:118-
29 616 23.doi:10.1111/j.1524-4733.2008.00400.x
30 617 52 Miller TA. Health literacy and adherence to medical treatment in chronic and acute illness: A meta-
31 618 analysis. *Patient Educ Couns* 2016;**99**:1079-86.doi:10.1016/j.pec.2016.01.020
32 619 53 Lam WY, Fresco P. Medication Adherence Measures: An Overview. *Biomed Res Int*
33 620 2015;**2015**:217047.doi:10.1155/2015/217047
34 621 54 Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment
35 622 adherence. *Med Pharm Rep* 2019;**92**:117-22.doi:10.15386/mpr-1201
36 623 55 Chew LD, Griffin JM, Partin MR, et al. Validation of screening questions for limited health literacy in a
37 624 large VA outpatient population. *J Gen Intern Med* 2008;**23**:561-6.doi:10.1007/s11606-008-0520-5
38 625 56 Health Literacy Tool Shed, 2020. Available: <https://healthliteracy.bu.edu>. [Accessed 17 August 2020].
39 626 57 McRae-Clark AL, Baker NL, Sonne SC, et al. Concordance of Direct and Indirect Measures of
40 627 Medication Adherence in A Treatment Trial for Cannabis Dependence. *J Subst Abuse Treat* 2015;**57**:70-
41 628 4.doi:10.1016/j.jsat.2015.05.002
42 629 58 Lim ML, van Schooten KS, Radford KA, et al. Association between health literacy and physical activity
43 630 in older people: a systematic review and meta-analysis. *Health Promot Int*
44 631 2020;**daaa072**.doi:10.1093/heapro/daaa072
45
46
47
48
49
50
51 632

52
53 **Figure 1. PRISMA Flow Diagram**

54 Notes: *no HL measure available (n=184), NVS (n=35), REALM (n=63), TOFHLA (n=90), other performance-based measure (n=5)

55 **only for samples that not exclusively focus on elders
56
57
58
59
60

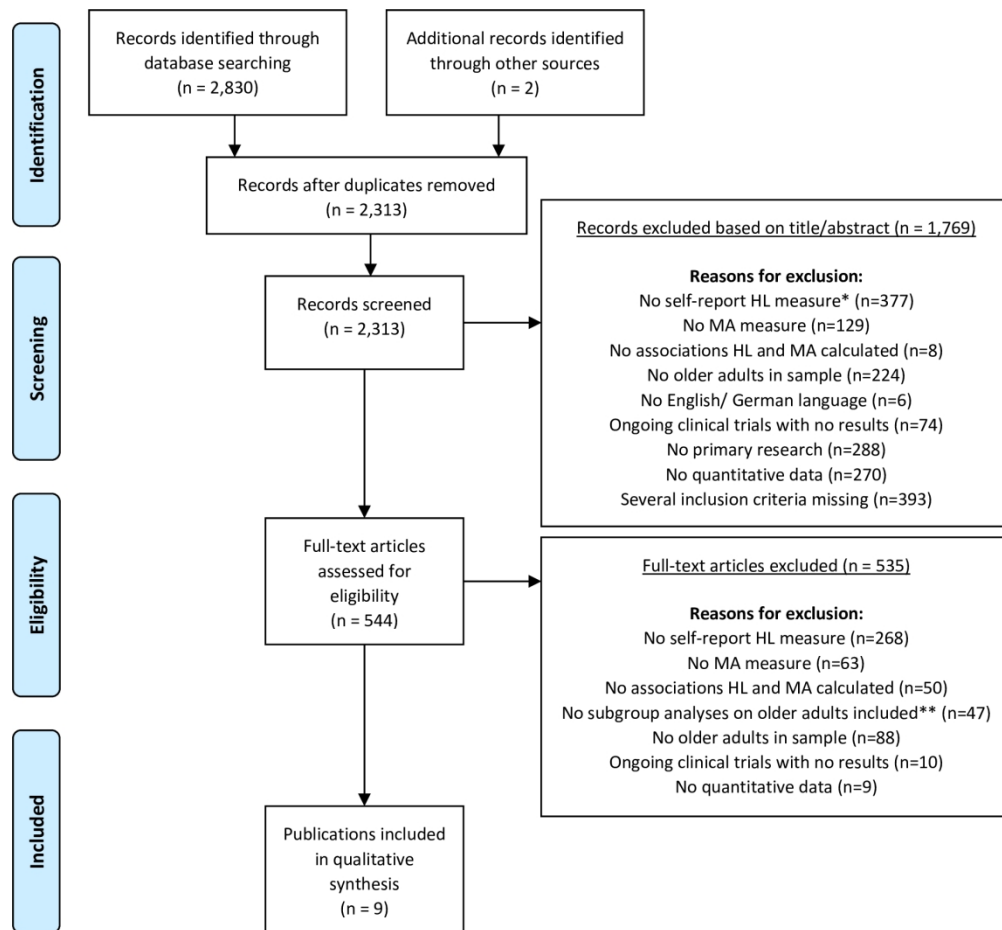


Figure 1. PRISMA Flow Diagram

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/>

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, Department 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

1
2
3 "patient adherence"[All Fields]) OR ("adherence"[All Fields] OR "adhere"[All Fields] OR
4 "adhered"[All Fields] OR "adherence"[All Fields] OR "adherences"[All Fields] OR
5 "adherent"[All Fields] OR "adherents"[All Fields] OR "adherer"[All Fields] OR
6 "adherers"[All Fields] OR "adheres"[All Fields] OR "adhering"[All Fields]) OR "non-
7 adherence"[All Fields] OR ("nonadherence"[All Fields] OR "nonadherent"[All Fields] OR
8 "nonadherents"[All Fields] OR "nonadherers"[All Fields]) OR ("medication
9 adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR
10 "medication adherence"[All Fields]) OR ("discontinuance"[All Fields] OR
11 "discontinuances"[All Fields] OR "discontinued"[All Fields] OR "discontinuation"[All
12 Fields] OR "discontinuations"[All Fields] OR "discontinue"[All Fields] OR
13 "discontinued"[All Fields] OR "discontinuer"[All Fields] OR "discontinuers"[All Fields] OR
14 "discontinues"[All Fields] OR "discontinuing"[All Fields]) OR "non-compliance"[All Fields]
15 OR ("noncompliant"[All Fields] OR "noncompliers"[All Fields] OR "noncompliers"[All
16 Fields] OR "noncomplying"[All Fields] OR "patient compliance"[MeSH Terms] OR
17 ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields]
18 OR "noncompliance"[All Fields] OR "noncompliances"[All Fields]) OR ("terminal"[All
19 Fields] OR "terminal s"[All Fields] OR "terminally"[All Fields] OR "terminals"[All Fields]
20 OR "terminate"[All Fields] OR "terminated"[All Fields] OR "terminates"[All Fields] OR
21 "terminating"[All Fields] OR "termination"[All Fields] OR "terminations"[All Fields] OR
22 "terminator"[All Fields] OR "terminators"[All Fields]) OR ("refill"[All Fields] OR
23 "refillable"[All Fields] OR "refilled"[All Fields] OR "refilling"[All Fields] OR "refills"[All
24 Fields])) AND ("aged"[MeSH Terms] OR "aged"[All Fields] OR "old"[All Fields] OR
25 ("older"[All Fields] OR "olders"[All Fields]) OR ("aged"[MeSH Terms] OR "aged"[All
26 Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR
27 "elderlys"[All Fields]) OR ("geriatric"[All Fields] OR "geriatrics"[MeSH Terms] OR
28 "geriatrics"[All Fields]) OR "oldest"[All Fields] OR ("elder s"[All Fields] OR "elders"[All
29 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: ¹Total 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>.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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 <i>et al.</i> , 2013	BHLS 3 questions	<u>Range of overall HL scores:</u> 3-15 with higher scores indicating higher HL <u>Cutoff/ categories:</u> NA	MMAS-4	<u>Range of overall MA scores:</u> 0-4 with higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were dichotomized into nonadherence (scores ≤ 2) and adherence (scores ≥3)
Lee <i>et al.</i> , 2017	BHLS 15 questions	<u>Range of overall HL scores:</u> 15-75 with higher scores indicating higher HL <u>Cutoff/ categories:</u> NA	MMAS-8	<u>Range of overall MA scores:</u> 0-8 with higher scores indicating higher MA <u>Cutoff/ categories:</u> Scores were categorized into high (scores of 8), medium (scores 6-7), and low (scores ≤5) MA
Lu <i>et al.</i> , 2019	HLS-EU-Q16	<u>Range of overall HL scores:</u> 0-50 with higher scores indicating higher HL <u>Cutoff/ categories:</u> Scores ≤33 indicated limited HL, scores >34 indicated adequate HL	MOS-SAS	<u>Range of MA scores:</u> 0-5 with higher scores indicating higher MA <u>Cutoff/ categories:</u> Scores were dichotomized into adherence (scores ≥4) and nonadherence (scores ≥3)
Reading <i>et al.</i> , 2019	BHLS 3 questions	<u>Range of overall HL scores:</u> 3-15 with higher scores indicating higher HL <u>Cutoff/ categories:</u> HL was dichotomized into adequate and inadequate, but no cutoffs were reported	CARDIA (3 questions)	<u>Range of MA scores:</u> NA <u>Cutoff/ categories:</u> 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 <i>et al.</i> , 2019	SILS	<u>Range of overall HL scores:</u> 1-5 with higher scores indicating lower HL <u>Cutoff/ categories:</u> HL scores ≥3 indicated inadequate HL and scores ≤2 indicated adequate HL	MMAS-4	<u>Range of overall MA scores:</u> 0-4 with higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were dichotomized into nonadherence (scores ≤ 3) and adherence (scores of 4)
Seong <i>et al.</i> , 2019	BHLS 3 questions	<u>Range of overall HL scores:</u> 0-12 with higher scores indicating higher HL <u>Cutoff/ categories:</u> 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?")	<u>Range of overall MA scores:</u> 1-5 with higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were dichotomized into nonadherence (scores ≤ 5) and adherence (scores of 6)
Shehadeh-Sheeny <i>et al.</i> , 2013	FCCHL	<u>Range of overall HL scores:</u> NA, higher scores indicating higher HL <u>Cutoff/ categories:</u> HL scores were categorized into low, medium, and high HL, but no cut offs were reported/ are available	MPR	<u>Range of overall MA scores:</u> 0-1 (0%-100%), higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were categorized into low (MPR ≤ 0.2) and high (MPR ≥ 0.8) MA

1					
2					
3	Song & Park, 2020	BHLS 15 questions	<u>Range of overall HL scores:</u> 15-75 with higher scores indicating higher HL	MMAS-8	<u>Range of overall MA scores:</u> 0-8 with higher scores indicating higher MA
4					
5			<u>Cutoff/ categories:</u>		<u>Cutoff/ categories:</u>
6			NA		NA
7	Wannasirikul <i>et al.</i> , 2016	FCCHL	<u>Range of overall HL scores:</u> 17-68 with higher scores indicating higher HL	ARMS	<u>Range of overall MA scores:</u> 14-56 with higher scores indicating higher MA
8					
9			<u>Cutoff/ categories:</u>		<u>Cutoff/ categories:</u>
10			HL scores were categorized into inadequate, marginal, and		NA
11			adequate HL, but no cut offs were reported/ are available		

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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3 **1 Self-reported health literacy and medication adherence in older adults: A systematic review**

4 2 Schönfeld MS¹, Pfisterer-Heise S², Bergelt C^{1,3}

5 3

6
7
8 ¹Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg,
9 Germany

10 ²Department of Biochemistry and Molecular Cell Biology, University Medical Centre Hamburg-
11 Eppendorf, Hamburg, Germany

12 ³Department of Medical Psychology, University Medicine Greifswald, Greifswald, Germany

13
14
15 **Corresponding author:**

16 **Moritz Sebastian Schönfeld**

17 University Medical Centre Hamburg-Eppendorf

18 Department of Medical Psychology

19 Martinistrasse 52

20 20246 Hamburg

21 Germany

22 mo.schoenfeld@uke.de

23 Tel: +49-40-7410-59140

24
25
26 4

27
28 **5 Word count**

29 6 5529 words

30
31
32 **8 Date and version**

33 9 First submission of manuscript: October 29, 2020

34 10 1. Resubmission of revised manuscript: August 10, 2021

35 11 2. Resubmission of revised manuscript: August 26, 2021

36 12 3. Resubmission of revised manuscript: October 1, 2021

37 13 4. Resubmission of revised manuscript: November 10, 2021

38
39
40 14

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 $\geq 66\%$ 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.

56 INTRODUCTION

57 Within the last decades, demographic change and increasing life expectancy have put older adults (≥ 60
58 years old as defined by the United Nations¹) in the focus of health care research. With increasing age, the
59 risk of chronic diseases and comorbidities rises resulting in a growing number of necessary treatments
60 (e.g. medication), and adherence to these treatments becomes crucial to reduce adverse reactions and
61 ensure safe and effective care. In this context, health literacy (HL), often defined as “the degree to which
62 individuals have the capacity to obtain, process, and understand basic health information and services
63 needed to make appropriate health decisions”², has been identified as a key influencing factor of
64 improving health-related behaviour in the elderly³. Accordingly, (elderly) people with low levels of HL use
65 health care more often and show higher rates of hospitalization than those with high levels of HL^{3,4}.

66 Research also confirmed low HL as a predictor of poor health outcomes linking lower HL to higher age⁵
67 ⁶, lower income⁵ and lower education^{3,7}. In addition, HL has been repeatedly linked to medication
68 adherence, commonly defined as “the extent to which a patient’s behaviour corresponds with the
69 prescribed medication dosing regime, including time, dosing and interval of medication intake”⁸.
70 Medication adherence (MA) has been the focus of this research since the number of medications taken
71 commonly increases with increasing age, making medication the most common form of therapy in the
72 elderly, often resulting in polypharmacy^{9,10}. Thus, MA still plays a crucial role in the elderly patient’s care.
73 However, research into the associations between HL and MA stays inconclusive¹¹⁻¹⁶. While multiple studies
74 report (significantly) positive associations between HL and MA¹⁷⁻²¹, others report (significantly) negative
75 associations^{22,23}.

76 Systematic reviews specifically conducted to analyse the relationship between HL and MA in the
77 elderly resulted in mixed findings as they often included studies with a variety of populations and measures
78 of HL^{12,16,24}. Older adults have commonly been examined as a homogenous group not taking into account
79 possible differences in levels of HL and MA between subgroups of age (e.g. 65-70 years old, 71-75 years
80 old, 76-80 years old, 85+ years old^{6,25}). In addition, reviews and meta-analyses examining the associations
81 between HL and MA in older age commonly included samples with a wide age range only focusing on the
82 mean age of samples. Since these samples often include (undisclosed) proportions of younger adults and
83 subgroups are not reported, results may not adequately reflect the relationship between HL and MA in
84 older adults^{24,26}. Previous reviews commonly aimed to include a wide selection of validated measures of
85 HL. However, since only a low proportion of relevant studies are measuring HL with self-reports, these
86 reviews often resulted in a focus on the so-called legacy instruments of HL (i.e. REALM²⁷, TOFHLA²⁸)^{12,24}
87 and thus included different measures and concepts of HL, which may have led to unknown bias^{15,26}. As
88 recently stated by Nguyen *et al.*²⁹, these often-deployed legacy tools may measure different aspects of
89 literacy and may not be appropriate to assess HL in older adults. Accordingly, limited HL was found to be
90 strongly associated with older age when measured with the TOFHLA (mainly assessing reading,
91 comprehension and numeracy skills²⁸) while limited HL had weak associations with older age³⁰ when
92 measured with the REALM (mainly assessing medical vocabulary²⁷).

93 As of late, these methodological shortcomings in research into HL have been increasingly recognized
94 leading to a broader discussion about the conceptualization and measurement of HL. Most recently,
95 researchers started concentrating on self-report measures of HL as new questionnaires from more
96 comprehensive concepts were developed (e.g. the HLS-EU-Q³¹). Compared to performance-based
97 measures, self-reports of HL commonly offer a fast, easy, and inexpensive way to collect data and have a
98 lower risk of stigma²⁹. Accordingly, self-reports present important advantages when assessing HL in

99 different populations and contexts as they can be applied more effortlessly. More recently, some studies
100 began to investigate levels of HL in different subgroups of older age resulting in a renewed call for more
101 differentiated methods and analyses in this population^{25 32}.

102 Thus, our review aims to systematically review the evidence on self-reported HL and MA in older adults
103 (≥ 60 years old) including: 1. the levels of self-reported HL and MA (if available, levels of different
104 subgroups); 2. the associations between self-reported HL and MA; 3. how self-reported HL and MA are
105 measured; and (if available) 4. moderator and mediator effects of other psychosocial factors.

106

107 **METHODS**

108 A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic
109 Reviews and Meta-Analyses (PRISMA) guidelines³³. A checklist of PRISMA items can be found in online
110 supplementary file S1. This review was registered with the International Prospective Register of Systematic
111 Reviews (PROSPERO): CRD42019141028. The protocol is presented in online supplementary file S2.

112

113 **Eligibility criteria**

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

117 **Intervention.** No specific interventions were included in the criteria. Nevertheless, only studies that
118 assessed associations (e.g. correlation, effect size) between self-reported HL and MA were deemed
119 eligible. Studies that assessed HL solely with a performance-based test instrument (e.g. REALM²⁷,
120 TOFHLA²⁸) were excluded from this review.

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

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

126

127 **Data sources and search strategy**

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

1
2
3 139 In addition, reference lists from eligible articles were hand searched accordingly. All references were
4 140 subsequently imported into Endnote X8 reference management software for screening purposes.
5
6 141

7 142 **Study selection and screening**

8 143 After removal of duplicates, two raters (MSS, SPH) screened titles and abstracts of all remaining studies
9 144 for eligibility. A checklist was developed for this purpose which included a list of inclusion and exclusion
10 145 criteria, such as type of measure of HL, MA, and included sample, to allow for a careful screening process.
11 146 As many studies include HL only as a secondary outcome and may thus not state it in the study's title or
12 147 abstract, a more liberal title/ abstract screening was conducted. Accordingly, two raters (MSS, SPH)
13 148 assessed the full texts of all previously screened studies independently. Figure 1 shows specific reasons for
14 149 study exclusion, which included lack of self-report HL measure, lack of MA measure, lack of associations
15 150 between HL and MA, lack of older adults in sample, lack of English or German language, being an ongoing
16 151 clinical trial with no results, lack of primary research (e.g. book chapter), lack of quantitative data (e.g.
17 152 interview study), or several of these reasons. In case of discrepancies, conflicts were discussed until
18 153 consensus was reached.
19
20 154

21 155 **Quality assessment**

22 156 The methodological quality of all studies included in this review was assessed using the NIH Quality
23 157 Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, NIH³⁴). Since only baseline
24 158 data from quantitative research was included, the NHLBI was deemed appropriate. The NHLBI contains 14
25 159 criteria mainly to assess the internal validity of a study. Each item was answered "yes" (if criterion was
26 160 met), "no" (if criterion was not met) or "cannot determine/ not applicable/ not reported". As the NHLBI is
27 161 not meant to assess the study quality by simply summing up its scores, an overall quality rating ("good",
28 162 "fair", "poor") for each study included a comprehensive and critical appraisal of each criterion as well as
29 163 the study as a whole. This included e.g. the number of participants, the precision of the findings, and the
30 164 risk of bias of the included studies.
31
32 165

33 166 **Data extraction and synthesis**

34 167 All relevant data was extracted by the first author with the help of a data extraction checklist that was
35 168 developed for this purpose and contained the following information about each included study: title,
36 169 authors, year published, study design and setting, sample and sample size, age subgroups, definition and
37 170 assessment of HL and MA, moderator and mediator effects (if available), statistical measures to calculate
38 171 associations between HL and MA (e.g. correlation), statistical significance if available.

39 172 As the studies showed heterogeneity due to differences in study design, participants, risk of bias, and
40 173 operationalization of HL and MA (e.g. different use of cutoffs and levels of HL), a narrative synthesis was
41 174 applied to analyse the studies thematically.
42
43 175

44 176 **Patient and public involvement**

45 177 Patients or the public were not involved in this study.
46
47 178

48 179 **RESULTS**

180
181 **Search results**
182 The literature search resulted in a total of 2,313 studies after removal of duplicates. After screening for
183 title and abstract another 1,769 studies were excluded based on exclusion criteria (figure 1). Full texts of
184 544 studies were screened and nine publications from eight studies met all eligibility criteria and were
185 thus included in this review (figure 1). The main reason for study exclusion in the screening process was
186 lack of self-reports of HL measure.

187
188 **Study characteristics**
189 Overall study characteristics are presented in table 1. All included publications were published between
190 2013 and 2020 with sample sizes between n=116 and n=12,159 (Median=293). The proportion of female
191 participants ranged from 33% to 100% (Median=53.6%). All studies adopted a cross-sectional design (5
192 survey studies). Three studies (four publications) were conducted in South Korea, and one study each in
193 China, USA, Pakistan, Israel, and Thailand. Studies were conducted across settings of tertiary care hospitals
194 (n=5), primary health care (n=1), private health care centres (n=1), community health care centres (n=1),
195 and clinics (n=1). All studies examined patients/adults with different types of (chronic) diseases:
196 hypertension (n=2), heart diseases (n=1), atrial fibrillation (n=2), osteoporosis (n=1), several chronic
197 diseases (n=3). Due to eligibility criteria restricting included samples to those with ≥66% of older adults
198 (60 years of age and older), all studies focused on the elderly and only two studies also included patients
199 younger than 60 years (table 1). Five studies included samples with a higher proportion of women.

200
201 **Quality assessment**
202 Study quality in terms of methodological quality and risk of bias was considered poor for one publication
203 and fair for eight publications (online supplementary table S2). In most cases, low study quality occurred
204 from lack of randomization, blinding, and longitudinal data. Accordingly, results in this review should be
205 interpreted with caution.

206
207 **Health literacy – key findings**
208 In five publications from four studies³⁵⁻³⁹ self-reported HL was measured using a selection of questions
209 from the Brief Health Literacy Screen (BHLS⁴⁰). The BHLS employs three to fifteen questions (e.g. “How
210 often do you have someone help you read hospital materials?”) to identify people with inadequate levels
211 of HL. Another study⁴¹ used the short version of the European Health Literacy Survey Questionnaire (HLS-
212 EU-Q) which was designed by the HLS-EU-Consortium based on a conceptual framework of HL³¹. One study
213 assessed HL with the Single Item Literacy Screener (SILS), which asks ““How often do you need to have
214 someone help when you read instructions, pamphlets, or other written material from your doctor or
215 pharmacy?”⁴². Another two studies adopted the Functional, Communicative, and Critical Health Literacy
216 questionnaire (FCCHL) developed by Ishikawa *et al.*⁴³, a validated questionnaire that assesses three areas
217 of HL: functional HL, communicative HL, and critical HL.

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

1
2
3 223 calculated HL scores. Five of these six studies^{38 41 44-46} found that a majority of the respective samples
4 224 reported limited HL levels (i.e. more people had low scores of HL; range from 62.6% to 92.5%,
5 225 Median=74.5%) whereas one study³⁷ found that a majority of the sample reported adequate levels of HL
6 226 (i.e. more people had high scores of HL; 76.9%).
7 227

8 228 **Medication adherence – key findings**

9
10 229 Four publications from three studies^{35 36 39 44} employed versions of the Morisky Medication Adherence
11 230 Scale (MMAS⁴⁷) to assess MA. The MMAS consists of four to eight questions asking about different aspects
12 231 of medication intake behaviour (e.g. “Do you sometimes forget to take your medication?”⁴⁷). One study⁴¹
13 232 used the Medical Outcomes Study Specific Adherence Scale (MOS-SAS⁴⁸) which addresses MA (“How often
14 233 have you done each of the following in the past 4 weeks: Took medication as prescribed (on time without
15 234 skipping dosis?)” as well as heart-healthy lifestyle behaviour (i.e. six preventive behaviours for coronary
16 235 heart disease, e.g. low-salt diet). One study³⁸ used a single-item adopted from Wu *et al.*⁴⁹ to assess MA
17 236 (“In the past week, have you forgotten to take your antithrombotic medication for various reasons?”).
18 237 Another study³⁷ adopted three questions from the Coronary Artery Risk Development in Young Adults
19 238 (CARDIA⁵⁰) to assess MA (1. “In the past month, how often did you take your medications as the doctor
20 239 prescribed?”; 2. “In the past month, how often did you forget to take 1 or more of your prescribed
21 240 medications?”; 3. “In the past month, how often did you decide to skip 1 or more of your prescribed
22 241 medications?”). MA was also assessed by the Medication Possession Ratio (MPR) in one study⁴⁵. The MPR
23 242 commonly represents the period during which a patient has an adequate amount of supply of his/her
24 243 medication available over a predefined amount of time (e.g. a year). One study assessed MA with the
25 244 Adherence to Refills and Medication Scale (ARMS⁵¹) which assesses if a patient can correctly take and refill
26 245 his or her medication on schedule.

27
28
29
30
31
32
33 246 Overall, five publications from four studies^{35 36 38 44 45} found that a majority of the sample reported low
34 247 levels of MA (i.e. more non-adherers; range from 50.2% to 69.4%, Median=59.0%) while three studies^{37 41}
35 248 ⁴⁶ in contrast, found that a majority of the sample reported high levels of MA (i.e. more adherers; range
36 249 from 84.7% to 98.3%, Median=93.7%). One study reported a sample mean score of MA only³⁹.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1. Overall summary of included studies

Authors, year	Setting, country	Sample				Disease	Methodological quality ¹
		N	Age (years), mean (±SD)	% Female	Age subgroups		
Lee <i>et al.</i> , 2013 ³⁵	Tertiary care hospitals, South Korea	n=293	65+ M=74.4 (6.3)	46.8%	NA	Chronic Diseases	fair
Lee <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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, NIH³⁴, 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 studies⁴¹ 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 study³⁷ 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 study³⁹ reported higher MA in 65-69-year-old adults compared to 70-79-year-old adults and ≥80-year-old adults. Another study³⁸ 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 study⁴¹ 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 <i>et al.</i> , 2013 ³⁵	NA	None conducted
Lee <i>et al.</i> , 2017 ³⁶	65-74 (57.0%) ≥75 (43.0%)	No significant differences in MA between age groups ($\chi^2=0.391$, $p=0.835$)
Lu <i>et al.</i> , 2019 ⁴¹	≤60 (21.5%) 61-70 (43.0%) 71-80 (29.7%) >81 (5.7%)	<p>Patients with limited HL were significantly older than those with adequate HL ($p<0.05$)</p> <p>Age was not a significant predictor for limited HL in ≥81-year-old patients compared to</p> <ul style="list-style-type: none"> - 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), $p=0.955$) <p>Age was not a significant predictor for medication nonadherence in ≥81-year-old patients compared to</p> <ul style="list-style-type: none"> - 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 <i>et al.</i> , 2019 ³⁷	<65 (27.2%) 65-74 (30.8%) 75-84 (30.5%) ≥85 (11.5%)	<p>Nonadherence to medication significantly differed according to age ($p<0.001$)</p> <p>Age was a significant predictor for nonadherence to medication in <65-year-old patients compared to</p> <ul style="list-style-type: none"> - 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), $p<0.001$) <p>Age was not a significant predictor for nonadherence to medication in <65-year-old patients compared to</p> <ul style="list-style-type: none"> - patients ≥85 years old (AOR (95% CI) = 0.86 (0.64-1.16), n.s.)
Saqlain <i>et</i>	65-75 (84.7%)	No significant differences in MA between age groups ($\chi^2=1.631$, $p=0.442$)

<i>al.</i> , 2019 ⁴⁴	76-85 (11.1%) >85 (4.2%)	
Seong <i>et al.</i> , 2019 ³⁸	65-70 (32.1%) 70-79 (45.5%) ≥80 (22.4%)	Adherence to medication significantly differed with respect to age ($\chi^2=15.15$, $p<0.001$) 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 <i>et al.</i> , 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 <i>et al.</i> , 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 study³⁸ reported mixed findings. In detail, one of two publications³⁵ from one study confirmed HL as the strongest predictor for MA in a hierarchical regression analysis while another publication³⁵ 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 study⁴¹ 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 fibrillation³⁷, 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 hypertension⁴⁴ found positive and statistically

1
2
3 289 significant associations between HL and MA as well as a higher likelihood of patients with adequate levels
4 290 of HL to be adherent to medication compared to patients with inadequate levels of HL. In their multivariate
5 291 logistic regression, the same study found that in addition to adequate HL, self-reported good and
6 292 moderate subjective health as well as independence in activities of daily living were also independent
7 293 predictors of MA in the elderly. Another study³⁸ reported significant differences in adherence to
8 294 antithrombotic medication by levels of HL but did not confirm HL as a significant predictor for MA in older
9 295 adults. They concluded that a significant association between HL and MA might exist still since in their
10 296 univariate regression the rate of inadequate HL was higher in the group of nonadherent patients compared
11 297 to adherent patients. However, in their multivariate logistic regression, the authors³⁸ found only cognitive
12 298 impairment to be a significant predictor of medication nonadherence in older patients with atrial
13 299 fibrillation. One study⁴⁵ found no significant association between HL and MA in a population of female
14 300 osteoporosis patients and found only self-reported income to be a significant predictor of adherence in
15 301 the conducted multivariate logistic regression. Another study³⁹ found significantly positive associations
16 302 between HL and MA. In their multiple regression analysis, the authors also found that income, number of
17 303 chronic diseases, vision problems, and HL were significant predictors of MA. One other study⁴⁶ analysed
18 304 the relationship between HL, MA, and blood pressure levels in primary care patients with hypertension
19 305 using a Structural Equation Modeling (SEM) approach, which supported the existence of a causal
20 306 relationship between these factors. Accordingly, HL had a positive but small statistically significant direct
21 307 effect on MA. Literacy and cognitive ability had the biggest direct effects on both HL and MA. Additionally,
22 308 HL had the biggest significantly negative direct effect on blood pressure levels (i.e. the higher the HL, the
23 309 lower the blood pressure level). Based on the SEM, the authors of this study⁴⁶ suggested a mediator effect
24 310 of HL on MA, even though no analysis was conducted. None of the other studies performed mediator
25 311 and/or moderator analyses concerning HL and/or MA and other factors

1
2
3 312
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

For peer review only

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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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)

1						
2						
3	Saqlain <i>et al.</i> , 2019 ⁴⁴	n=262, 65+ years	SILS	MMAS-4	n=98 (37.4%) patients had adequate HL	Positive and statistically significant associations between HL and MA ($\chi^2=24.356$, $p<0.001$)
4						
5		M=NA			n=102 (38.9%) patients were adherent to medication	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), $p<0.001$)
6						
7		Outpatients with				
8		hypertension from tertiary				
9		health care centres in				
10		Islamabad, Pakistan				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), $p<0.002$)
11	Seong <i>et al.</i> , 2019 ³⁸	n=277, 65+ years	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	Positive and statistically significant associations between HL and MA ($\chi^2=22.00$, $p<0.001$)
12						
13		M=74.2 (7.2)				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), $p=0.002$)
14		Outpatients with atrial				
15		fibrillation undergoing				
16		antithrombotic therapy in				
17		tertiary general hospital in				
18		South Korea			n=139 (50.2%) patients were nonadherent to medication	
19					Significant differences in MA between age subgroups ($p<0.001$)	
20	Shehadeh- Sheeny <i>et al.</i> , 2013 ⁴⁵	n=303, 60+ years	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	No significant associations between MA and HL ($p=0.44$)
21						
22		M= 71 (6.04)				46.7% of patients with high HL were more adherent to medication compared to 35.9% of patients with low HL
23						
24		Female Arab patients				
25		with osteoporosis				
26		from three clinics in Israel			n=125 (41.3%) patients had high MA	In multivariate logistic regression only self-reported income was a significant predictor of MA (OR (95% CI) = 1.26 (1.01-1.58), $p=0.037$)
27	Song & Park, 2020 ³⁹	n=116, 65+ years	BHLS 15 questions	MMAS-8	Mean HL was 42.4 (6.6)	HL positively correlated with MA ($r=0.42$, $p<0.001$)
28						
29		M=72.7 (6.1)				In multiple regression analysis HL was significant predictor of MA ($\beta=0.23$, $p<0.001$)
30		Community-dwelling older			Mean MA was at a medium level (M=4.3 (2.2))	Other significant predictors of MA were income ($\beta=0.35$, $p<0.001$), number of chronic diseases ($\beta=-0.33$, $p<0.001$), and vision problems ($\beta=-0.32$, $p<0.001$)
31		adults in health care				
32		centre, South Korea				
33						
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Wannasirikul <i>et al.</i> , 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 ($\beta=0.08$, $p<0.05$) Cognitive ability ($\beta=0.22$, $p<0.05$) and literacy ($\beta=0.46$, $p<0.05$) had biggest and significantly positive direct effect on MA Literacy ($\beta=0.15$, $p<0.05$) and cognitive ability ($\beta=0.52$, $p<0.05$) had biggest and significantly positive direct effect on HL HL had biggest significantly negative direct effect on blood pressure level ($\beta=-0.14$, $p<0.05$) MA had a significantly negative direct effect on blood pressure level ($\beta=-0.02$, $p<0.05$) 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 advantages²⁹. 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 review²⁴ 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 intelligence²⁹. 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

1
2
3 358 association with adherence. Since empirical data on possible associations between literacy and self-
4 359 reported HL are still widely lacking, we need more research to explore and develop comprehensive
5 360 theories in this area.

7 361 Six studies^{37 38 41 44-46} included in this review found that a majority of participants in the respective
8 362 samples reported limited (i.e. inadequate, low, marginal) HL. This is consistent with other research that
9 363 showed that older people commonly reach only low levels of self-reported health literacy^{3 25 32} even though
11 364 this research is very scarce. HL was measured by versions of four different self-reports (BHLS^{40 55}, HLS-EU-
12 365 Q³, SILS⁴², FCCHL⁴³). This shows that self-reporting HL measures are still rarely utilized when examining
13 366 older adults, even though the Health literacy Tool Shed⁵⁶ lists 29 self-report instruments for HL in English
14 367 alone (58 without language restrictions).

16 368 MA was assessed through self-reports in all but one of the included studies^{35-39 41 44 46}. Nevertheless,
17 369 we recommend a more detailed description of operationalization of MA as many studies still use the
18 370 concepts of adherence and compliance interchangeably. Interestingly, we had to exclude many studies
19 371 from this review even though they assessed some form of adherence, because they only included
20 372 measures of general preventive behaviour (e.g. physical activity) and not MA. However, the use of such
21 373 secondary adherence measures might be a promising approach to get a more comprehensive picture of
22 374 adherence in older adults⁵⁴. Especially a multi-method approach could be helpful since self-reported
23 375 adherence may also be affected by cognitive bias and/or social desirability in older adults. As such, the
24 376 utilization of both direct (e.g. laboratory measures) and indirect (e.g. self-reports) measures of
25 377 adherence^{54 57} may help to get a better understanding of adherence and its associations with self-reported
26 378 HL in older adults. A number of studies in this review also included measures of secondary prevention (e.g.
27 379 physical activity, heart-healthy lifestyle behavior) as well as other factors (e.g. income, cognitive ability)
28 380 providing further knowledge on possible confounders in the mechanisms between HL and MA.
29 381 Accordingly, several studies confirmed multiple other factors as predictors for MA (e.g., health status^{36 37}
30 382 ⁴⁴, income^{39 45}, physical activity^{37 44}, cognitive ability^{38 46}) and/ or HL (e.g., cognitive ability⁴⁶, stress
31 383 management⁴¹). In a recent systematic review and meta-analysis by Lim et al.⁵⁸, the authors examined the
32 384 associations between physical activity and HL and found that older adults with inadequate levels of HL
33 385 were “[...] less likely [...] to report engaging in physical activity [...]” than those with adequate HL, showing
34 386 the importance of also addressing secondary adherence measures in future research in this area. Notably,
35 387 their review also included younger adults (samples with mean age ≥55 years) and different of HL measures
36 388 (legacy measures and self-reports).

43 389 Even though we also encourage researchers to assess HL with a multi-method approach (e.g.
44 390 subjective and objective instruments), we suggest a more rigorous differentiation in analysis and
45 391 interpretation when comparing HL measures that are based on different concepts (e.g. legacy tools and
46 392 self-reports). This may also help to clarify further the associations between self-reported HL and literacy
47 393 as measured by legacy instruments. As stated by Nguyen *et al.*²⁹, a separation in analyses of objective and
48 394 subjective measures of HL as well as a closer alignment of HL theory and measurement could help clarify
49 395 the relationship between HL and MA. This idea was also supported by one of the studies³⁹ included in this
50 396 review, which aimed at comparing two different measures of HL (self-report vs. legacy measure). The
51 397 authors found that even though both measures were significantly and positively correlated to MA, only
52 398 the self-report was a significant predictor for MA in older adults suggesting that self-reports may be more
53 399 fitting to access HL when predicting MA since “[...] assessing older adults’ experiences of limited health
54 400 literacy is more appropriate for catching any decreased medication adherence [...]”.

1
2
3 401 This review additionally confirms that age subgroup analyses are conducted very rarely for self-
4 402 reported HL but quite often for MA. This may result from the fact that research on MA in the elderly is
5 403 traditionally older than research on HL in the elderly and with regard to HL most studies still treat older
6 404 people as a homogenous group²⁵. Most studies in this review did not find any significant associations
7 405 between age and MA and only two studies^{37 39} reported significant differences in MA between age
8 406 subgroups. Accordingly, one study³⁷ reported that young/ young-old people (21-65 years old) were more
9 407 likely not to adhere to their medication compared to old/older adults (65-84 years old) but not oldest
10 408 adults (≥ 85 years old). A second study³⁹ reported higher MA in 65-69-year-old adults compared to
11 409 older/oldest adults (70-90 years old). Not surprisingly, only one study conducted analyses on the
12 410 relationship between age and HL⁴¹, showing that patients with limited HL were significantly older
13 411 compared to those with adequate HL. Even though generalizability is very limited, these results reveal the
14 412 necessity for more differentiated analyses (e.g. of subgroups) in future HL and MA research on older
15 413 adults. In context of demographic change and increasing life expectancy, more differentiated analyses
16 414 could help to understand specific needs and barriers of elderly (patient) populations with different chronic
17 415 diseases. Importantly, definitions of *old age* are often inconsistent and include people from ages 60, 65,
18 416 or 70 years and over. These dissimilarities in the definitions of old age may result from differences in
19 417 cultural and/or economic standards (e.g. USA vs. Asia) and often manifest in different demographic
20 418 changes and/or different life expectancies thus resulting in a different quality of health care in groups of
21 419 older adults. Consequently, when looking at older adults' health care and health outcomes, it is critical to
22 420 include contextual aspects such as cultural or economic standards.

23 421 Studies in this review show some inconsistencies in the use of cutoffs, use, and wording of HL levels.
24 422 Of all included studies, six studies^{37 38 41 44-46} reported categories of HL (e.g. adequate) of which only three³⁸
25 423 ^{41 44} reported cutoffs for these categories. Three publications^{35 36 39} from two studies reported neither
26 424 categories nor cutoffs for HL and only five publications^{35 36 38 39 46} from four studies reported mean values
27 425 of HL. For example, Shehadeh-Sheeny et al. calculated scores for low, medium, and high levels of HL while
28 426 Wannasirikul et al. calculated scores for adequate, marginal, and inadequate HL levels even though no
29 427 cutoffs were reported/available by neither the authors nor the FCCHL measure both studies used. The
30 428 inconsistent use of cutoffs and wording may indicate a lack of certainty and experience in the application
31 429 of self-reports enhancing the call for more differentiated research and the development of easy-to-use
32 430 but still valid tools.

33 431
34 432 **Strength and limitations**
35 433 The strengths of this study include the exhaustive methodology and comprehensive search strategy that
36 434 were used. As we followed a strict screening procedure, we are confident that we found all eligible studies.
37 435 Since we excluded all studies that measured HL with performance-based instruments, we aimed to reduce
38 436 bias resulting from fundamental differences in constructs and concepts. Although we see this exclusion as
39 437 a considerable advantage, we cannot eliminate the possibility of bias still resulting from theoretical or
40 438 practical differences in self-reports as some of them are built on more complex conceptual frameworks
41 439 than others. Additionally, there are advantages in assessing HL in older adults with self-reports since they
42 440 reduce the possible bias of performance-based measures resulting from fear of stigma and/or (time)

1
2
3 441 pressure. Nevertheless, we recognize the inherent limitations of self-reporting tools that may also have
4 442 biased our results.

5 443 Other limitations should be considered. All studies included in this review were cross-sectional, thus
6 444 we cannot determine any direction of causality. The fair to poor methodological quality of the included
7 445 studies may also increase the risk of (unknown) bias. Given the heterogeneity of the studies, a meta-
8 446 analysis (e.g. pooled odds ratios) could not be conducted, thus limiting further understanding of the
9 447 relationship between HL and MA in older adults. Accordingly, certainty of evidence of these results is low.
10 448 Additionally, our search strategy in this review limited included studies to English and German, which could
11 449 bias results due to missing research in other languages. Finally, we were not able to include EMBASE as a
12 450 database in our search. Even though, we are very confident that we did not miss a substantial amount of
13 451 literature, this must be considered as a limitation of this review.
14
15
16
17
18

19 452

20 21 453 **CONCLUSIONS**

22 454 Based on a rather high level of uncertainty, included literature in this review suggests that self-reported
23 455 HL and MA in older adults show a somewhat straightforward positive association. While previous research
24 456 on HL and MA in older adults did not always find clear associations, many studies included in this review
25 457 reported significantly positive associations between HL and MA. In addition, HL plays an important role as
26 458 a predictor of MA in older adults as several studies in this review could confirm. However, other factors
27 459 (e.g. cognitive ability) appear equally important in predicting MA in older adults, and future studies should
28 460 also focus on secondary adherence measures (e.g. physical activity) when examining the associations
29 461 between HL and MA in the elderly. Finally, study heterogeneity and methodological weaknesses reveal a
30 462 definitive need for more differentiated research regarding different definitions, concepts, and measures
31 463 of HL and MA as well as longitudinal research designs and studies that analyse age subgroups in older
32 464 adults.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 465 **Acknowledgements**

4 466 We would like to thank Dr. rer. biol. hum. Laura Inhestern for her advice during the preparation of the
5 467 search for this review.
6 468

7 469 **Author Contributions**

8 470 All authors were involved in the design and planning of the review. MSS prepared, performed, and
9 471 redefined the searches after consultation with SPH and CB. MSS and SPH performed screening and data
10 472 extraction with the help of CB in case of disagreements or discussion. All authors contributed to the data
11 473 analysis and interpretation. MSS wrote the first draft which was critically revised by SPH and CB.
12 474

13 475 **Ethics Approval Statement**

14 476 This study does not involve human participants, as it is a systematic review.
15 477

16 478 **Funding**

17 479 This research received no specific grant from any funding agency in the public, commercial or not-for-
18 480 profit sectors.
19 481

20 482 **Competing interests**

21 483 None declared.
22 484

23 485 **Patient consent**

24 486 Not required.
25 487

26 488 **Provenance and peer review**

27 489 Not commissioned; externally peer reviewed.
28 490

29 491 **Data sharing statement**

30 492 All data relevant to the study are included in the article or uploaded as supplementary information.
31 493

32 494 **Open Access**

33 495 This is an open access article distributed in accordance with the Creative Commons Attribution Non
34 496 Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work
35 497 non-commercially, and license their derivative works on different terms, provided the original work is
36 498 properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial.
37 See: <http://creativecommons.org/licenses/by-nc/4.0/>.

499 **REFERENCES**

- 500 1 United Nations, Department of Economic and Social Affairs, Population Division. World Population
501 Ageing 2019: Highlights (ST/ESA/SER.A/430). 2019.
- 502 2 Ratzan SC, Parker RM. Health literacy - identification and response. *J Health Commun* 2006;**11**:713-
503 5.doi:10.1080/10810730601031090
- 504 3 Consortium H-E. Comparative Report on Health Literacy in Eight EU Member States. The European
505 Health Literacy Project 2009–2012. Vienna: Ludwig Boltzmann Institute for Health Promotion Research
506 2012.
- 507 4 Berkman ND, Sheridan SL, Donahue KE, et al. Low health literacy and health outcomes: an updated
508 systematic review. *Ann Intern Med* 2011;**155**:97-107.doi:10.7326/0003-4819-155-2-201107190-00005
- 509 5 Chesser AK, Keene Woods N, Smothers K, et al. Health Literacy and Older Adults: A Systematic Review.
510 *Gerontol Geriatr Med* 2016;**2**:2333721416630492.doi:10.1177/2333721416630492
- 511 6 Vogt D, Schaeffer D, Messer M, et al. Health literacy in old age: results of a German cross-sectional
512 study. *Health Promot Int* 2018;**33**:739-47.doi:10.1093/heapro/dax012
- 513 7 Wolf MS, Feinglass J, Thompson J, et al. In search of 'low health literacy': threshold vs. gradient effect
514 of literacy on health status and mortality. *Soc Sci Med* 2010;**70**:1335-
515 41.doi:10.1016/j.socscimed.2009.12.013
- 516 8 Gast A, Mathes T. Medication adherence influencing factors—an (updated) overview of systematic
517 reviews. *Systematic Reviews* 2019;**8**:1-17.doi:10.1186/s13643-019-1014-8
- 518 9 Hoel RW, Giddings Connolly RM, Takahashi PY. Polypharmacy Management in Older Patients. *Mayo*
519 *Clinic Proceedings* 2021;**96**:242-56.doi:10.1016/j.mayocp.2020.06.012
- 520 10 Chiatti C, Bustacchini S, Furneri G, et al. The economic burden of inappropriate drug prescribing, lack
521 of adherence and compliance, adverse drug events in older people: a systematic review. *Drug Saf*
522 2012;**35 Suppl 1**:73-87.doi:10.1007/BF03319105
- 523 11 Huang YM, Shiyabola OO, Smith PD. Association of health literacy and medication self-efficacy with
524 medication adherence and diabetes control. *Patient Prefer Adherence* 2018;**12**:793-
525 802.doi:10.2147/PPA.S153312
- 526 12 Martins NFF, Abreu DPG, Silva BTD, et al. Functional health literacy and adherence to the medication
527 in older adults: integrative review. *Rev Bras Enferm* 2017;**70**:868-74.doi:10.1590/0034-7167-2016-0625
- 528 13 Park NH, Song MS, Shin SY, et al. The effects of medication adherence and health literacy on health-
529 related quality of life in older people with hypertension. *Int J Older People Nurs*
530 2018;**13**:e12196.doi:10.1111/opn.12196
- 531 14 Roh YH, Koh YD, Noh JH, et al. Effect of health literacy on adherence to osteoporosis treatment
532 among patients with distal radius fracture. *Arch Osteoporos* 2017;**12**:42.doi:10.1007/s11657-017-0337-0
- 533 15 Zhang NJ, Terry A, McHorney CA. Impact of health literacy on medication adherence: a systematic
534 review and meta-analysis. *Ann Pharmacother* 2014;**48**:741-51.doi:10.1177/1060028014526562
- 535 16 Ostini R, Kairuz T. Investigating the association between health literacy and non-adherence.
536 *International journal of clinical pharmacy* 2014;**36**:36-44.doi:10.1007/s11096-013-9895-4
- 537 17 Lindquist LA, Go L, Fleisher J, et al. Relationship of health literacy to intentional and unintentional
538 non-adherence of hospital discharge medications. *J Gen Intern Med* 2012;**27**:173-8.doi:10.1007/s11606-
539 011-1886-3
- 540 18 Wolf MS, Davis TC, Osborn CY, et al. Literacy, self-efficacy, and HIV medication adherence. *Patient*
541 *Educ Couns* 2007;**65**:253-60.doi:10.1016/j.pec.2006.08.006
- 542 19 Kripalani S, Gatti ME, Jacobson TA. Association of age, health literacy, and medication management
543 strategies with cardiovascular medication adherence. *Patient Educ Couns* 2010;**81**:177-
544 81.doi:10.1016/j.pec.2010.04.030
- 545 20 Bauer AM, Schillinger D, Parker MM, et al. Health literacy and antidepressant medication adherence
546 among adults with diabetes: the diabetes study of Northern California (DISTANCE). *J Gen Intern Med*
547 2013;**28**:1181-7.doi:10.1007/s11606-013-2402-8

- 1
2
3 548 21 Mayo-Gamble TL, Mouton C. Examining the Association Between Health Literacy and Medication
4 549 Adherence Among Older Adults. *Health Commun* 2018;**33**:1124-30.doi:10.1080/10410236.2017.1331311
5 550 22 Mosher HJ, Lund BC, Kripalani S, et al. Association of health literacy with medication knowledge,
6 551 adherence, and adverse drug events among elderly veterans. *J Health Commun* 2012;**17 Suppl 3**:241-
7 552 51.doi:10.1080/10810730.2012.712611
8 553 23 Fang MC, Machtinger EL, Wang F, et al. Health literacy and anticoagulation-related outcomes among
9 554 patients taking warfarin. *J Gen Intern Med* 2006;**21**:841-6.doi:10.1111/j.1525-1497.2006.00537.x
10 555 24 Loke YK, Hinz I, Wang X, et al. Systematic review of consistency between adherence to cardiovascular
11 556 or diabetes medication and health literacy in older adults. *Ann Pharmacother* 2012;**46**:863-
12 557 72.doi:10.1345/aph.1Q718
13 558 25 Vogt D, Berens EM, Schaeffer D. Gesundheitskompetenz im höheren Lebensalter [Health Literacy in
14 559 Advanced Age]. *Gesundheitswesen* 2020;**82**:407-12.doi:10.1055/a-0667-8382
15 560 26 Geboers B, Brainard JS, Loke YK, et al. The association of health literacy with adherence in older
16 561 adults, and its role in interventions: a systematic meta-review. *BMC Public Health*
17 562 2015;**15**:903.doi:10.1186/s12889-015-2251-y
18 563 27 Davis TC, Long SW, Jackson RH, et al. Rapid estimate of adult literacy in medicine: a shortened
19 564 screening instrument. *Fam Med* 1993;**25**:391-5
20 565 28 Parker RM, Baker DW, Williams MV, et al. The test of functional health literacy in adults: a new
21 566 instrument for measuring patients' literacy skills. *J Gen Intern Med* 1995;**10**:537-
22 567 41.doi:10.1007/BF02640361
23 568 29 Nguyen TH, Paasche-Orlow MK, McCormack LA. The state of the science of health literacy
24 569 measurement. *Information Services & Use* 2017;**37**:189-203.doi:10.3233/ISU-170827
25 570 30 Kobayashi LC, Wardle J, Wolf MS, et al. Aging and Functional Health Literacy: A Systematic Review
26 571 and Meta-Analysis. *J Gerontol B Psychol Sci Soc Sci* 2016;**71**:445-57.doi:10.1093/geronb/gbu161
27 572 31 Sørensen K, Van den Broucke S, Pelikan JM, et al. Measuring health literacy in populations:
28 573 illuminating the design and development process of the European Health Literacy Survey Questionnaire
29 574 (HLS-EU-Q). *BMC Public Health* 2013;**13**:948.doi:10.1186/1471-2458-13-948
30 575 32 Berens EM, Vogt D, Messer M, et al. Health literacy among different age groups in Germany: results
31 576 of a cross-sectional survey. *BMC Public Health* 2016;**16**:1151.doi:10.1186/s12889-016-3810-6
32 577 33 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-
33 578 analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.doi:10.1371/journal.pmed.1000097
34 579 34 National Heart, Lung, and Blood Institute.. Quality Assessment Tool for Observational Cohort and
35 580 Cross-Sectional Studies, 2014. Available: [https://www.nhlbi.nih.gov/health-pro/guidelines/in-](https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort)
36 581 [develop/cardiovascular-risk-reduction/tools/cohort](https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort) [Accessed 05 May 2020].
37 582 35 Lee SK, Kang BY, Kim HG, et al. Predictors of medication adherence in elderly patients with chronic
38 583 diseases using support vector machine models. *Healthc Inform Res* 2013;**19**:33-
39 584 41.doi:10.4258/hir.2013.19.1.33
40 585 36 Lee YM, Yu HY, You MA, et al. Impact of health literacy on medication adherence in older people with
41 586 chronic diseases. *Collegian* 2017;**24**:11-8.doi:10.1016/j.colegn.2015.08.003
42 587 37 Reading SR, Black MH, Singer DE, et al. Risk factors for medication non-adherence among atrial
43 588 fibrillation patients. *BMC Cardiovasc Disord* 2019;**19**:38.doi:10.1186/s12872-019-1019-1
44 589 38 Seong HJ, Lee K, Kim BH, et al. Cognitive Impairment Is Independently Associated with Non-
45 590 Adherence to Antithrombotic Therapy in Older Patients with Atrial Fibrillation. *Int J Environ Res Public*
46 591 *Health* 2019;**16**.doi:10.3390/ijerph16152698
47 592 39 Song MS, Park S. Comparing two health literacy measurements used for assessing older adults'
48 593 medication adherence. *J Clin Nurs* 2020;**29**:4313-20.doi:10.1111/jocn.15468
49 594 40 Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy.
50 595 *Fam Med* 2004;**36**:588-94

- 1
2
3 596 41 Lu M, Ma J, Lin Y, et al. Relationship between patient's health literacy and adherence to coronary
4 597 heart disease secondary prevention measures. *J Clin Nurs* 2019;**28**:2833-43.doi:10.1111/jocn.14865
5 598 42 Morris NS, MacLean CD, Chew LD, et al. The Single Item Literacy Screener: evaluation of a brief
6 599 instrument to identify limited reading ability. *BMC Fam Pract* 2006;**7**:21.doi:10.1186/1471-2296-7-21
7 600 43 Ishikawa H, Takeuchi T, Yano E. Measuring functional, communicative, and critical health literacy
8 601 among diabetic patients. *Diabetes Care* 2008;**31**:874-9.doi:10.2337/dc07-1932
9 602 44 Saqlain M, Riaz A, Malik MN, et al. Medication Adherence and Its Association with Health Literacy
10 603 and Performance in Activities of Daily Livings among Elderly Hypertensive Patients in Islamabad,
11 604 Pakistan. *Medicina (Kaunas)* 2019;**55**.doi:10.3390/medicina55050163
12 605 45 Shehadeh-Sheeny A, Eilat-Tsanani S, Bishara E, et al. Knowledge and health literacy are not
13 606 associated with osteoporotic medication adherence, however income is, in Arab postmenopausal
14 607 women. *Patient Educ Couns* 2013;**93**:282-8.doi:10.1016/j.pec.2013.06.014
15 608 46 Wannasirikul P, Termsirikulchai L, Sujirarat D, et al. Health Literacy, Medication Adherence, and
16 609 Blood Pressure Level among Hypertensive Older Adults Treated at Primary Health Care Centers.
17 610 *Southeast Asian J Trop Med Public Health* 2016;**47**:109-20
18 611 47 Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of
19 612 medication adherence. *Med Care* 1986;**24**:67-74.doi:10.1097/00005650-198601000-00007
20 613 48 Sherbourne CD, Hays RD, Ordway L, et al. Antecedents of adherence to medical recommendations:
21 614 results from the Medical Outcomes Study. *J Behav Med* 1992;**15**:447-68.doi:10.1007/BF00844941
22 615 49 Wu JR, DeWalt DA, Baker DW, et al. A single-item self-report medication adherence question predicts
23 616 hospitalisation and death in patients with heart failure. *J Clin Nurs* 2014;**23**:2554-
24 617 64.doi:10.1111/jocn.12471
25 618 50 Cutter GR, Burke GL, Dyer AR, et al. Cardiovascular risk factors in young adults. The CARDIA baseline
26 619 monograph. *Control Clin Trials* 1991;**12**:1S-77S.doi:10.1016/0197-2456(91)90002-4
27 620 51 Kripalani S, Risser J, Gatti ME, et al. Development and evaluation of the Adherence to Refills and
28 621 Medications Scale (ARMS) among low-literacy patients with chronic disease. *Value Health* 2009;**12**:118-
29 622 23.doi:10.1111/j.1524-4733.2008.00400.x
30 623 52 Miller TA. Health literacy and adherence to medical treatment in chronic and acute illness: A meta-
31 624 analysis. *Patient Educ Couns* 2016;**99**:1079-86.doi:10.1016/j.pec.2016.01.020
32 625 53 Lam WY, Fresco P. Medication Adherence Measures: An Overview. *Biomed Res Int*
33 626 2015;**2015**:217047.doi:10.1155/2015/217047
34 627 54 Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment
35 628 adherence. *Med Pharm Rep* 2019;**92**:117-22.doi:10.15386/mpr-1201
36 629 55 Chew LD, Griffin JM, Partin MR, et al. Validation of screening questions for limited health literacy in a
37 630 large VA outpatient population. *J Gen Intern Med* 2008;**23**:561-6.doi:10.1007/s11606-008-0520-5
38 631 56 Health Literacy Tool Shed, 2020. Available: <https://healthliteracy.bu.edu>. [Accessed 17 August 2020].
39 632 57 McRae-Clark AL, Baker NL, Sonne SC, et al. Concordance of Direct and Indirect Measures of
40 633 Medication Adherence in A Treatment Trial for Cannabis Dependence. *J Subst Abuse Treat* 2015;**57**:70-
41 634 4.doi:10.1016/j.jsat.2015.05.002
42 635 58 Lim ML, van Schooten KS, Radford KA, et al. Association between health literacy and physical activity
43 636 in older people: a systematic review and meta-analysis. *Health Promot Int*
44 637 2020;**daaa072**.doi:10.1093/heapro/daaa072
45
46
47
48
49
50
51 638

52
53 **Figure 1. PRISMA Flow Diagram**

54 Notes: *no HL measure available (n=184), NVS (n=35), REALM (n=63), TOFHLA (n=90), other performance-based measure (n=5)

55 **only for samples that not exclusively focus on elders
56
57
58
59
60

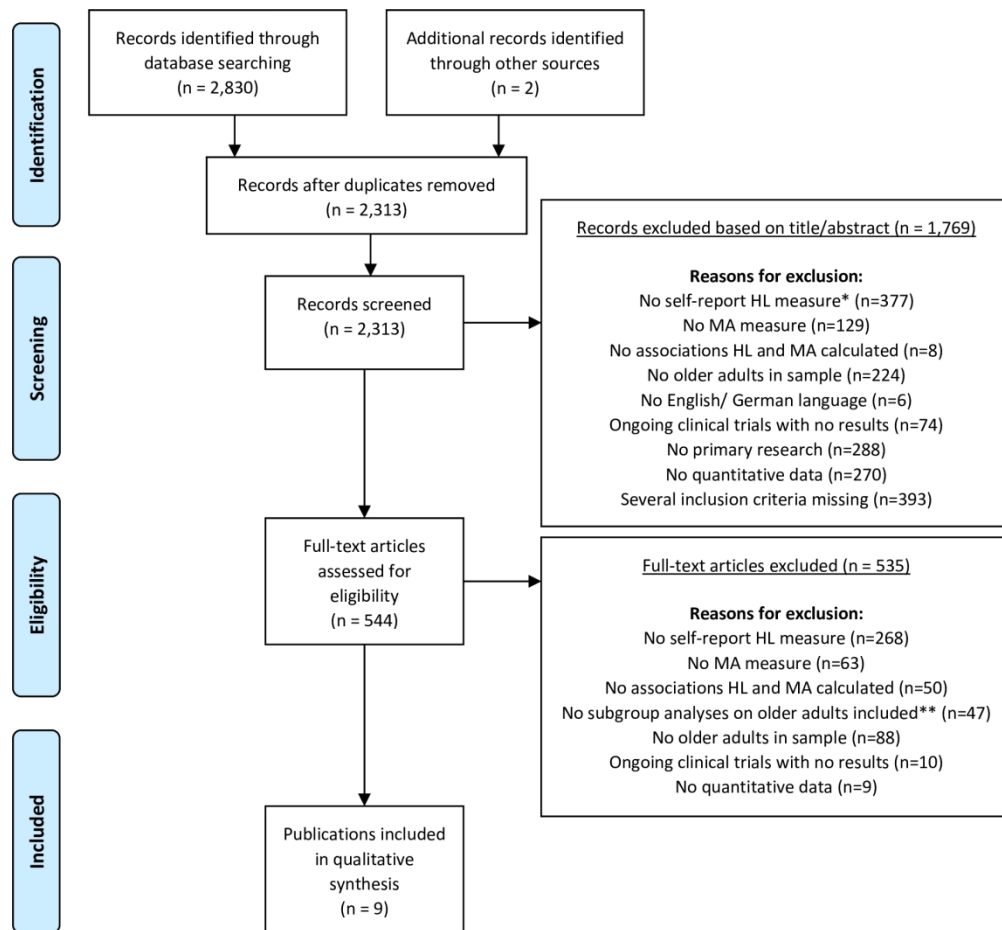


Figure 1. PRISMA Flow Diagram

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/>

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, Department 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

1
2
3 "patient adherence"[All Fields]) OR ("adherence"[All Fields] OR "adhere"[All Fields] OR
4 "adhered"[All Fields] OR "adherence"[All Fields] OR "adherences"[All Fields] OR
5 "adherent"[All Fields] OR "adherents"[All Fields] OR "adherer"[All Fields] OR
6 "adherers"[All Fields] OR "adheres"[All Fields] OR "adhering"[All Fields]) OR "non-
7 adherence"[All Fields] OR ("nonadherence"[All Fields] OR "nonadherent"[All Fields] OR
8 "nonadherents"[All Fields] OR "nonadherers"[All Fields]) OR ("medication
9 adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR
10 "medication adherence"[All Fields]) OR ("discontinuance"[All Fields] OR
11 "discontinuances"[All Fields] OR "discontinued"[All Fields] OR "discontinuation"[All
12 Fields] OR "discontinuations"[All Fields] OR "discontinue"[All Fields] OR
13 "discontinued"[All Fields] OR "discontinuer"[All Fields] OR "discontinuers"[All Fields] OR
14 "discontinues"[All Fields] OR "discontinuing"[All Fields]) OR "non-compliance"[All Fields]
15 OR ("noncompliant"[All Fields] OR "noncompliers"[All Fields] OR "noncompliers"[All
16 Fields] OR "noncomplying"[All Fields] OR "patient compliance"[MeSH Terms] OR
17 ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields]
18 OR "noncompliance"[All Fields] OR "noncompliances"[All Fields]) OR ("terminal"[All
19 Fields] OR "terminal s"[All Fields] OR "terminally"[All Fields] OR "terminals"[All Fields]
20 OR "terminate"[All Fields] OR "terminated"[All Fields] OR "terminates"[All Fields] OR
21 "terminating"[All Fields] OR "termination"[All Fields] OR "terminations"[All Fields] OR
22 "terminator"[All Fields] OR "terminators"[All Fields]) OR ("refill"[All Fields] OR
23 "refillable"[All Fields] OR "refilled"[All Fields] OR "refilling"[All Fields] OR "refills"[All
24 Fields])) AND ("aged"[MeSH Terms] OR "aged"[All Fields] OR "old"[All Fields] OR
25 ("older"[All Fields] OR "olders"[All Fields]) OR ("aged"[MeSH Terms] OR "aged"[All
26 Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR
27 "elderlys"[All Fields]) OR ("geriatric"[All Fields] OR "geriatrics"[MeSH Terms] OR
28 "geriatrics"[All Fields]) OR "oldest"[All Fields] OR ("elder s"[All Fields] OR "elders"[All
29 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: ¹Total 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 <i>et al.</i> , 2013	BHLS 3 questions	<u>Range of overall HL scores:</u> 3-15 with higher scores indicating higher HL <u>Cutoff/ categories:</u> NA	MMAS-4	<u>Range of overall MA scores:</u> 0-4 with higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were dichotomized into nonadherence (scores ≤ 2) and adherence (scores ≥3)
Lee <i>et al.</i> , 2017	BHLS 15 questions	<u>Range of overall HL scores:</u> 15-75 with higher scores indicating higher HL <u>Cutoff/ categories:</u> NA	MMAS-8	<u>Range of overall MA scores:</u> 0-8 with higher scores indicating higher MA <u>Cutoff/ categories:</u> Scores were categorized into high (scores of 8), medium (scores 6-7), and low (scores ≤5) MA
Lu <i>et al.</i> , 2019	HLS-EU-Q16	<u>Range of overall HL scores:</u> 0-50 with higher scores indicating higher HL <u>Cutoff/ categories:</u> Scores ≤33 indicated limited HL, scores >34 indicated adequate HL	MOS-SAS	<u>Range of MA scores:</u> 0-5 with higher scores indicating higher MA <u>Cutoff/ categories:</u> Scores were dichotomized into adherence (scores ≥4) and nonadherence (scores ≥3)
Reading <i>et al.</i> , 2019	BHLS 3 questions	<u>Range of overall HL scores:</u> 3-15 with higher scores indicating higher HL <u>Cutoff/ categories:</u> HL was dichotomized into adequate and inadequate, but no cutoffs were reported	CARDIA (3 questions)	<u>Range of MA scores:</u> NA <u>Cutoff/ categories:</u> 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 <i>et al.</i> , 2019	SILS	<u>Range of overall HL scores:</u> 1-5 with higher scores indicating lower HL <u>Cutoff/ categories:</u> HL scores ≥3 indicated inadequate HL and scores ≤2 indicated adequate HL	MMAS-4	<u>Range of overall MA scores:</u> 0-4 with higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were dichotomized into nonadherence (scores ≤ 3) and adherence (scores of 4)
Seong <i>et al.</i> , 2019	BHLS 3 questions	<u>Range of overall HL scores:</u> 0-12 with higher scores indicating higher HL <u>Cutoff/ categories:</u> 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?")	<u>Range of overall MA scores:</u> 1-5 with higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were dichotomized into nonadherence (scores ≤ 5) and adherence (scores of 6)
Shehadeh-Sheeny <i>et al.</i> , 2013	FCCHL	<u>Range of overall HL scores:</u> NA, higher scores indicating higher HL <u>Cutoff/ categories:</u> HL scores were categorized into low, medium, and high HL, but no cut offs were reported/ are available	MPR	<u>Range of overall MA scores:</u> 0-1 (0%-100%), higher scores indicating higher MA <u>Cutoff/ categories:</u> MA scores were categorized into low (MPR ≤ 0.2) and high (MPR ≥ 0.8) MA

1					
2					
3	Song & Park, 2020	BHLS 15 questions	<u>Range of overall HL scores:</u> 15-75 with higher scores indicating higher HL	MMAS-8	<u>Range of overall MA scores:</u> 0-8 with higher scores indicating higher MA
4					
5			<u>Cutoff/ categories:</u>		<u>Cutoff/ categories:</u>
6			NA		NA
7	Wannasirikul et al., 2016	FCCHL	<u>Range of overall HL scores:</u> 17-68 with higher scores indicating higher HL	ARMS	<u>Range of overall MA scores:</u> 14-56 with higher scores indicating higher MA
8					
9			<u>Cutoff/ categories:</u>		<u>Cutoff/ categories:</u>
10			HL scores were categorized into inadequate, marginal, and		NA
11			adequate HL, but no cut offs were reported/ are available		

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.