Title

Health literacy and patient outcomes in chronic kidney disease: a systematic review

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Abstract

Background: Limited health literacy affects 25% of people with Chronic Kidney Disease (CKD), and may reduce self-management skills resulting in poorer clinical outcomes. By disproportionately affecting people with low socioeconomic status and non-white ethnicity, limited health literacy may promote health inequity.

Methods: Systematic review of quantitative studies of health literacy and clinical outcomes among adults with CKD.

Results: 29 studies (13 articles; 16 conference abstracts) were included. One included non-USA patients. Five were cohort studies, 24 cross-sectional. 18,300 patients were studied: 4,367 non-dialysis CKD; 13,202 dialysis, 390 transplant; 341 unspecified. Median study size was 127 (IQR: 92-238), but 480 (IQR: 260-2392) for cohort studies. Median proportion of non-white participants was 48% (IQR: 17-70%). Six health literacy measures were used. Outcomes included patient attributes, care processes, clinical/laboratory parameters, and 'hard' clinical outcomes. Limited health literacy was significantly, independently associated with hospitalisations, emergency department use, missed dialysis sessions, cardiovascular events and mortality (in cohort studies). Study quality was high (1 study), moderate (3 studies) and poor (25 studies), limited by sampling methods, variable adjustment for confounders and reduced methodological detail given in conference abstracts.

Conclusions: There is limited robust evidence of the causal effects of health literacy on patient outcomes in CKD. Available evidence suggests associations with adverse clinical events, increased healthcare use, and mortality. Prospective studies are required to determine the causal effects of health literacy on outcomes in CKD patients, and examine the relationships between socioeconomic status, comorbidity, health literacy and CKD outcomes. Intervention development and evaluation will determine whether health literacy is a modifiable determinant of poor outcomes in CKD.

Summary

This systematic review summarises evidence of the associations between limited health literacy and patient outcomes in chronic kidney disease. A wide variety of outcome measures were studied, including patient attributes, care processes, clinical and laboratory parameters and 'hard' clinical outcomes. Further prospective research is needed, notably among those with non-dialysis CKD, and to investigate the effects of low health literacy on important outcomes including access to kidney transplantation. Future research should aim to inform the development of interventions to improve outcomes among those with limited health literacy.

Introduction

Health Literacy is a personal attribute defined as the ability to access, understand and use health-related information [1]. Inadequate or 'limited' health literacy is associated with the development of long-term health conditions [2], reduced use of preventative medicine, poorer ability to manage medications and increased mortality [3, 4]. Health literacy is related to, but distinct from other concepts such as general literacy and patient activation [5]. The potential for communication-related interventions to improve understanding among those with limited health literacy and to positively impact upon clinical outcomes [6] has driven a rapid expansion of health literacy research, especially in chronic disease populations.

Patients with early Chronic Kidney Disease (CKD) are asked to take medications and alter their lifestyle in order to reduce the risk of cardiovascular disease and CKD progression. Those with advanced CKD are advised to prepare for renal replacement therapy (RRT) or conservative care [7]. Kidney transplantation provides the best biological outcomes for many patients with advanced CKD [8, 9], but access to kidney transplantation necessitates further clinical investigations and appointments, often in addition to time-consuming dialysis treatment. Throughout these care pathways, patients' motivation to engage with CKD-management activity will be influenced by their understanding of the risk of disease and the relative benefits of different treatments. The process of managing diet, medications and appointments will depend on adequate understanding of written and numerical instructions. As CKD progresses, the burden of disease-management activity increases, while the capacity of patients to cope may reduce because of increasing symptoms, comorbidities and reduced functional status [10]. Patients with limited health literacy may be more susceptible to becoming overburdened, resulting in reduced adherence to treatment and inferior clinical outcomes. Shared decision-making [11] and self-care initiatives aim to increase patient involvement, but adequate health literacy is likely to be required to successfully participate in these activities.

A 2017 systematic review showed that limited health literacy affects around a quarter of people with CKD and found associations with low socioeconomic status and non-white ethnicity [12]. Through these associations, limited health literacy has been implicated as a mediating factor in promoting inequity in health outcomes. The aim of this review was to summarise the evidence for associations between reduced health literacy and patient outcomes in CKD.

Subjects and Methods

The review protocol was registered with the international prospective register of systematic reviews

(http://www.crd.york.ac.uk/PROSPERO; reference: CRD42016049172).

DT and SF assessed English language studies of any design for inclusion by three criteria:

1. At least 50 adults over 18 with CKD were included

2. A validated tool was used to quantitatively describe an individual's overall health literacy on a single scale

3. Associations were tested between health literacy and health outcomes among patients with CKD

CKD was defined within studies by diagnosis code, estimated GFR calculation or requirement for RRT. Studies of fewer than 50 participants were excluded in order to identify those with quantitative rather than qualitative methodology.

Electronic databases were searched in August 2016. The databases used were Medline (1996 onwards), Embase (1980 onwards), OvidFullText (including PsychArticles, 1980 onwards), Health Management Information Consortium (1979 onwards), Cumulative Index to Nursing and Allied Health Literature, (CINAHL; 1981 onwards) and Psychinfo (1806 onwards). Search terms are detailed in the supplementary material, and were identical to those previously used in a review of health literacy prevalence and associations [12]. This was possible because the search strategy included a combination of health literacy- and CKD-specific terms without reference to prevalence, associations or outcomes. In contrast to the review of health literacy prevalence and associations, studies were not required to specify a prevalence value for limited health literacy. This allowed inclusion of studies where associations were found but prevalence was not reported, or studies examining associations between health literacy score as continuous measure and clinical outcomes. The health literacy measures used and definitions of limited health literacy are shown in Table 1.**Error! Reference source not found.**

Abstracts from the American Transplant Congress, World Transplantation Congress, International Congress of the Transplantation Society, National Kidney Federation, Australia and New Zealand Society of Nephrology and American Society of Transplant Surgeons were identified by the above database searches. In addition to database searches, abstract archives 2011-2016 from the UK Renal Association, European Renal Association/European Dialysis and

Transplant Association, International Society of Nephrology and American Society of Nephrology were searched separately for the terms 'health liter*' and 'literacy'.

Full texts of journal articles were obtained and reviewed if the first two inclusion criteria were met. Articles or conference abstracts were included if they met all three criteria. Conference abstracts were included only if they presented data not published elsewhere as a journal article. Authors were contacted for further information to establish if a study met the inclusion criteria, or to increase the quality of the review.

DT recorded and summarised the study characteristics, including study design, the health literacy measure used, sample size, demographics, definitions of any outcome measures, associations tested between health literacy and health outcomes in univariate and multivariate analyses, covariates included in multivariate models, and any significant associations which were found. Results from cohort studies were presented separately from the results of cross-sectional studies. Outcome measures were categorised as 'patient attributes', 'processes of care', 'clinical parameters', 'laboratory measures' and 'clinical outcomes.' These terms are defined in the headings of Table 2.

Measures of effect for associations between health literacy and outcomes in cohort studies were summarised, with 95% confidence intervals. Meta-analysis was not possible because of the diverse range of outcome measures tested. Study quality was assessed using a pre-agreed scoring system. DT and SF independently allocated scores dependent on study design, sample size, sample population, sampling methods and the potential for confounding of the results, and the combined scores were used to classify studies as 'low', 'moderate' or 'high' quality. This scoring was used as a guide to the two reviewers, who decided the final quality grading by discussion. Quality scoring is described in the supplementary material. Statistical significance was defined *a priori* as p<0.05, unless individual study methodology specified a different threshold.

Results

Figure 1 shows the study selection process. Twenty-nine studies were eligible for inclusion [13-41], summarised in Table 3. There was full agreement between the two reviewers as to which studies met the inclusion criteria. Thirteen published articles [13, 17, 19-24, 27, 38-41] and 16 conference abstracts [14-16, 18, 25, 26, 28-37] were included. Five were cohort studies (two published articles [17, 23] and three conference abstracts [18, 28, 36]); 24 were cross-

sectional studies, one of which was a pilot of an educational intervention with post-intervention measurement of outcomes. No case-control studies were identified. One study reported on patients from multiple countries (listed in caption to Table 3) [18]. All others reported exclusively on patients from the USA.

In total, 18,300 patients were studied, 14,682 of whom were included in five cohort studies. 4,367 patients from 12 studies had non-dialysis CKD. 13,202 dialysis patients were studied in 13 studies and 390 transplant patients were studied in three studies. Of the dialysis patients, a maximum of 84 received peritoneal dialysis. Three studies included patients at multiple treatment stages [14, 19, 27]. For two studies describing 341 patients [14, 27], subgroup data by treatment stage was not available. It was not possible to classify patients with non-dialysis CKD by CKD stage because of variation in the way these data were reported in individual studies. Median study sample size was 127 (IQR: 92- 238).

The health literacy measures used, and the associated definitions of limited health literacy are summarised in Table 1**Error! Reference source not found.**. Two studies used more than one measure.

Two studies included recruits to established clinical trials [23, 36]; the remainder selected patients from clinical environments without randomisation or measures to ensure a representative sample had been obtained. Twelve conference abstracts stated no exclusion criteria. Of 17 studies where exclusion criteria were available, 11 excluded non-English speakers and 11 excluded those with known cognitive impairment.

For 20 studies where data were available, mean or median age ranged from 47-72 years. For 23 studies where gender data were available, median proportion of male participants per study was 54% (IQR: 49.5-57.5). Ethnicity of participants was not stated for eight studies, but for the remaining 21 studies, the median proportion of non-white participants was 48% (IQR: 17-70). Study quality was graded as low for 25 studies, moderate for 3 studies [16, 18, 23] and high for one study [28].

In Table 2, the numerous outcome measures which were tested for association with health literacy are classified by type of outcome measure and the treatment stage of the study population. The results of univariate and multivariate analyses to test associations between outcome variables and limited health literacy (or health literacy as a continuous measure) are summarised in Table 4 and Table 5, along with covariates from multivariate models. Figure 2 shows effect sizes for associations tested in prospective analyses from cohort studies.

The five cohort studies (see Figure 2) had a median sample size of 480 (IQR: 260-2392) and follow up times between 12 and 42 months (unknown for one study) [18].

Two reported on patients with non-dialysis CKD [28, 36]. One study of 2,392 patients with CKD stage 1-4 showed independent associations between limited health literacy and hospitalisations and atherosclerotic events (defined as myocardial infarction, stroke or peripheral-vascular disease), with adjustment for SES, comorbidity and demographics. No association was found between health literacy and mortality in this study. Another cohort study showed a significant univariate association between limited health literacy and hazard of dialysis initiation among 74 patients with CKD3-4, but no significant difference in the rate of hospitalisation [36].

Three cohort studies reported on dialysis patients [17, 18, 23]. A study of 260 prevalent haemodialysis patients showed independent associations between limited health literacy and hospitalisations, missed dialysis sessions and ED attendances, after adjustment for demographics, income, and comorbidity [23]. There was no significant association with mortality in this study. Two other cohort studies showed independent associations between limited health literacy and mortality in 480 incident haemodialysis patients from the USA [17] and 11,476 prevalent haemodialysis patients from multiple countries [18]. One of these did not include adjustment for socioeconomic status [17] and the other did not include adjustment for comorbidity [18].

In results from cross-sectional studies, lower health literacy was independently associated with lower eGFR [20] and lower perceived [40] and objective [39] kidney disease knowledge among patients with non-dialysis CKD. Among dialysis patients, limited health literacy was independently associated with higher BP (diastolic and mean arterial pressure) [13] and longer time to transplant referral [24] after adjustment for demographics and socioeconomic status. An independent association between limited health literacy and dialysis catheter use was found in one study [16] without adjustment for socioeconomic status. This finding conflicted with another study showing higher fistula use among those with limited health literacy by univariate analysis [23]. Three other studies tested for an association between health literacy and type of haemodialysis access, but found no significant associations [17, 30, 35].

Discussion

To our knowledge, this is the first systematic review to explore associations between health literacy and clinical outcomes in CKD. We identified 29 studies of 18,300 patients, from which 14,682 patients were included in 5 cohort studies. In these cohort studies, low health literacy was associated with hospitalisations and cardiovascular events in non-dialysis CKD patients, and with reduced dialysis adherence, hospitalisation and mortality in dialysis patients. However, despite the large number of patients studied, robust evidence for a causal effect of health literacy on patient outcomes in CKD was limited. The majority of included studies were cross-sectional- the weakest study design for inferring causation. Studies of transplant patients and patients treated with peritoneal dialysis were especially limited. Although a wide variety of outcome measures were tested for association with health literacy, few studies assessed 'hard' clinical outcomes such as mortality or transplantation, focussing instead on surrogate outcome measures or processes of care. Further, the majority of studies were only available as conference abstracts, limiting the methodological detail available to allow in-depth assessment of study quality.

In **non-dialysis CKD** populations, patients with limited health literacy were found to have significantly lower disease knowledge and understanding of test results, after adjustment for educational level [31, 39, 40]. One cohort study reported increased risk of hospitalisations (Rate Ratio, RR: 1.40; 95% CI: 1.28-1.53) and atherosclerotic events (RR: 1.68; 95% CI: 1.10-2.58) among patients with limited health literacy compared to those with adequate health literacy [28]. These findings support the notion that reduced understanding of disease and treatment could reduce patients' ability to successfully control cardiovascular risk factors, with a resulting impact on clinical outcomes. Although one cross-sectional study reported lower eGFR among those with lower health literacy (and inferred an association with more rapid disease progression) [20], this finding was not supported by a high quality cohort study which found no significant association between limited health literacy and the incidence of ESRD (Hazard Ratio, HR: 1.10; 95% CI: 0.74-1.60) [28].

Dialysis patients with limited health literacy were found to be at increased risk of mortality compared to those with adequate health literacy in analyses from two cohort studies (HR: 1.54; 95% CI: 1.01-2.36 and HR: 1.65; 95% CI: 1.28-2.12) [17, 18], although one study lacked adjustment for comorbidity and the other lacked adjustment for socioeconomic status. A smaller cohort study with adjustment for both comorbidity and socioeconomic status [23] showed no association between limited health literacy and mortality, (HR: 0.96; 95% CI: 0.21-2.17). The same study

reported that patients with limited health literacy were at increased risk of missed dialysis sessions (RR: 2.14; 95% CI: 1.1-4.17), emergency department attendances (RR: 1.37; 94% CI: 1.01-1.86) and ESRD-related hospital admissions (RR: 1.55; 95% CI: 1.03-2.34), after adjustment for comorbidity and socioeconomic variables (see Figure 2 and Table 5). These findings are consistent with hypotheses that by impairing patients' understanding of their disease and its treatment, low health literacy results in poorer treatment adherence and higher use of emergency care. Poorer adherence to treatment may also explain the observed in higher blood pressure among dialysis patients with lower health literacy [13]. There was no consensus from several studies on a relationship between limited health literacy and haemodialysis access [16, 17, 23, 30, 35]. Future studies of dialysis populations should focus on the effect of limited health literacy on referral to nephrology services, dialysis modality choice, dialysis quality measures, adverse events on dialysis and success with home therapies, including peritoneal dialysis.

This review highlights the paucity of research into the causal effects of limited health literacy on **kidney transplant** outcomes. One cross-sectional study showed reduced transplant-specific decision-making capacity among those with limited health literacy [27], and another showed reduced chance of referral for transplant evaluation (HR: 0.22; 95% CI: 0.08-0.60), although time-to-event data in this study were collected retrospectively, and subject to survivorship bias [24]. Kidney transplant recipients, especially recipients of living donor or pre-emptive transplants have significantly higher health literacy than dialysis patients [31, 42] and other surgical patients [43], suggesting that the process of selecting patients for transplantation favours those with higher health literacy. There is a need for prospective study of the causal effects of limited health literacy on access to transplant referral and listing, and on outcomes after transplantation.

In all patient groups, associations with a variety of outcomes in unadjusted analyses should be interpreted with caution because of the risk of confounding by SES and comorbidity, both of which are strongly associated with limited health literacy [12, 42].

In other healthcare settings, systematic reviews of health literacy and health outcomes report associations between limited health literacy and reduced medical knowledge [44], reduced use of preventative medicine, reduced ability to interpret written information or manage medications, increased risk of hospitalisation including emergency department use [45], lower health status, and increased mortality [3, 46]. The overall lack of research into the causal effect of limited health literacy on health outcomes is noted [3, 43]. The potential role of limited health literacy in

promoting inequity of health outcomes requires deeper investigation in other chronic disease populations as well as in CKD [47].

This review benefits from a broad search strategy including updated health literacy terms, and an extensive search of conference abstracts which identified many unpublished studies. There are several limitations. First, the majority of evidence came from the USA, which limits the application of findings to other healthcare systems. The impact of low health literacy on patients' ability to navigate healthcare systems would be expected to vary depending on the ease with which each healthcare system can be navigated. Arguably, insurance-based healthcare systems such as the US system may be more difficult to navigate than systems where healthcare is free at the point of use. Because of associations with low SES, patients with limited health literacy in the USA are more likely to be uninsured, with associated reduced access to care - this association could confound results. Second, the majority of evidence was from cross sectional studies, and sampling methods had potential to introduce bias: all but two studies used non-random sampling in clinical environments. Third, there was wide variation in the age, gender and ethnicity of participants, making comparison between studies difficult. Fourth, although we obtained additional information by contact with authors, the detail available was limited because 16 of 29 studies were only reported only as conference abstracts. However, inclusion of conference abstracts in the review demonstrates the volume of unpublished health literacy research which exists, (with negative studies possibly subject to publication bias), and allowed us to report preliminary results from large cohort studies whose publication is awaited [18, 28]. Fifth, differences between health literacy measures limits between-study comparability. The health literacy measures used included comprehension assessments such as REALM, STOFHLA and NVS, which directly assess individuals' understanding, and screening tools such as the BHLS, which record patient-reported understanding. Although screening measures have been validated against comprehension assessments [48], sensitivity and specificity to detect limited health literacy is reduced. Health literacy measures also differ in the aspects of health literacy measured: the NVS is the only measure used here to directly assess numeracy, which may influence ability to manage medications and keep appointments. Last, although this review was registered with the international prospective register of systematic reviews, data collection had already begun at the time of registration.

Around 25% of people with CKD have limited health literacy , which disproportionally affects those with low socioeconomic status and of non-white Ethnicity, and appears to increase the risk of inferior clinical outcomes. As a

potential mediator of the association between low socioeconomic status and outcomes, health literacy may be a target for interventions to reduce socioeconomic and demographic inequity in CKD outcomes. Educational interventions for those with low health literacy have been shown in other healthcare settings to improve comprehension, and have potential to improve outcomes [49]. In CKD care, enhanced education at first nephrology contact may confer a deeper understanding of the risks associated with CKD, resulting in improved self-management. Ensuring adequate understanding of the relative advantages of different forms of RRT may facilitate shared decision-making, improve treatment adherence and reduce inequity in access to transplantation. The development of such interventions will be informed by a Cochrane review of current health literacy interventions in CKD [50], and by further prospective research into the associations between limited health literacy and CKD outcomes. Research from outside the USA is required to ensure that results are applicable to other populations and healthcare systems. The interlinked relationships between health literacy, socioeconomic status and comorbidity should be considered, and mediation pathways examined [51]. Related patient attributes such as patient activation [5] and capacity [10] may also dictate success in self-management, and should be considered when developing health literacy-related interventions. Testing of complex interventions should aim to establish the extent to which reduced health literacy is modifiable in different patient groups (non-dialysis, dialysis, transplant), ideally by randomised controlled trial using mixed qualitative and quantitative methods. Successful interventions would improve communication, understanding and patient satisfaction, resulting in improved clinical outcomes and cost-effectiveness.

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Conflict of interest statement

The results presented in this paper have not been published previously in whole or in part. Any conflicts of interest are listed below:

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Authors' contributions

DT performed the literature searches, compiled the tables and figures and was the primary author of the article. DT and SF screened the results of literature searches, identified studies for inclusion and assessed study quality. RR and PR were supervising authors. CD, GO and CT edited the manuscript further.

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Tables

Table 1: Health lIteracy measures used in studies included in this review. HL: Health literacy

Health Literacy measure	Number of studies using measure (%)	Form	Approximate time taken	Health literacy categorisation
Short Test of Functional HL in Adults (STOFHLA)	10 (34)	36 reading comprehension items- select from four choices to replace missing words in text (modified Cloze procedure)	12 minutes	0-22 Limited 23-36: Adequate
Rapid Estimate of Adult HL in Medicine (REALM)	9 (31)	125 health-related words (66 in more commonly used form) tested for pronunciation accuracy	3 minutes	0-44 Inadequate 45-60: Marginal 61-66: Adequate (Limited= Inadequate + marginal)
REALM-T (Transplant-specific version of REALM)	2 (7)	69 kidney transplant-related terms tested for pronunciation accuracy	3 minutes	Not clearly defined
REALM-SF (Short Form of REALM)	3 (10)	7 health-related words tested for pronunciation accuracy	2-3 minutes	0-3 Inadequate 4-6 Marginal 7 Adequate
Brief HL Screen (BHLS)	3 (10)	Three questions: How confident are you filling out forms by yourself? How often do you have someone help you read hospital materials? How often do you have problems learning about your medical condition because of difficulty reading hospital materials? All graded 1-5, scores range 3-15 (or 0-12 in one study [18])	<1 minute	3-8 (or 0-5): Lower 9-14 (or 6-12): Moderate/Higher (<10/15 or <6/12 indicates limited HL)
Newest Vital Sign (NVS)	4 (14)	Six-item assessment of reading comprehension from an ice-cream nutrition label	6 minutes maximum (average 2.9 minutes) [52]	0-1: High likelihood marginal/inadequate 2-3: Possible marginal/inadequate 4-6: Adequate (Here, <4 deemed limited HL [20])

Table 2: Outcome variables tested for association with health literacy. Shading indicates variables tested in cohort studies.

	Patient attributes (Measured patient skills such as disease knowledge)	Processes of care (Clinical events not directly related to a clinical outcome)	Clinical parameters (Measured parameters which associated with improved clinical outcomes)	Lab measures (Lab values associated with clinical outcomes, including attainment of standards for dialysis quality)	Clinical outcomes
Non-dialysis CKD	Self-reported understanding of test results Objective kidney disease knowledge Perceived kidney disease knowledge Patient satisfaction with clinician communication Sodium knowledge Knowledge of restricted foods Awareness of CKD	Attendance vs non-attendance at transplant assessment	BP Tobacco use Waist-Hip ratio Body mass index Dietary intake	Lipids eGFR	Progression to ESRD Dialysis initiation Atherosclerotic event (MI, Stroke, PVD) Hospitalisation rate Mortality
Dialysis	Improvement in Dialysis/transplant knowledge after education Disaster preparedness Medication label understanding Decision-making capacity Medicines management capacity Self-reported medication adherence Dialysis knowledge	Infection episodes Hospitalisations ED attendances Missed dialysis sessions Attendance vs non-attendance at transplant assessment	BP Dialysis catheter use IDWG	Haemoglobin Haematocrit Transferrin Saturation Calcium Phosphate Intact Parathyroid Hormone Albumin Kt/V	Time to transplant referral Time to transplant listing Mortality Kidney transplantation
Transplant	Medication non-adherence (by survey measure) Decision-making capacity			Transplant function	

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Table 3: Summary characteristics of included studies.

α- Australia, New Zealand, Canada, UK, USA, Belgium, France, Countries of the former Gulf Cooperation Council (GCC), Germany, Italy, Japan, Russia, Span, Sweden, and Turkey.

CKD- Chronic Kidney Disease; HL-Health Literacy; LHL- Limited Health Literacy; HD- Haemodialysis; PD- Peritoneal Dialysis; CV- Cardiovascular; CVD: Cardiovascular disease; BP-Blood Pressure; BMI- Body Mass Index; Hct: haematocrit; Alb: serum albumin; Phos: serum phosphate; TS: transferrin saturation; iPTH: intact parathyroid hormone; MDRD: Modification of Diet in Renal Disease; Hb: haemoglobin; Ca: serum calcium; ED- Emergency Department; IDWG: Intra-dialytic weight gain.

	Study	Year	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Setting & recruitment method	Participants	Exclusion criteria	Health Literacy measure	Outcome variables tested	Follow-up time
Cohort studies	Cavanaugh 1 [17]	2010	480	62	56	Incident HD	Prevalence and associations of LHL and risk of all-cause mortality	Adults 'eligible for a patient education programme' from 77 US Dialysis units.	52% white 50% diabetic	<18; Non-permanent dialysis patients, Known cognitive impairment, Non-English speakers.	REALM	Mortality by adjusted hazard ratio. Hb, Ca, Kt/V, Hct. Alb, Phos, TS, iPTH	14-35 months (mortality) 12 months (lab values)
	Cavanaugh 2 [18] (abstract)	2015	11476	-	-	Prevalent HD	Assess International variation in HL and association with mortality	International sample from the DOPPS4 and DOPPS5 cohorts- randomly selected patients from dialysis units in participating countries α	-	None stated	BHLS (0-12)	Mortality by adjusted hazard ratio	Not stated
	Green [23]	2013	260	62	58	Prevalent HD	Examine associations of LHL with dialysis adherence and health resource use	Patients from 9 dialysis units included in an RCT of strategies for managing pain, sexual dysfunction and depression	40% Black	<18. Non-English speaking, cognitive dysfunction, considering switch to PD or planned LD transplant.	REALM	Hb, Ca, Phos, Alb, iPTH, Kt/V. Dialysis adherence, ED visits, ESRD-related hospitalisations. Kidney transplantation, mortality.	12-24 months
	Lora [28] (abstract)	2016	2392	-	-	Non-dialysis CKD1-4	Identify clinical outcomes associated with limited HL	Non-Hispanic Black and white	-	Hispanic patients	STOFHLA	Incident ESRD, Atherosclerotic events, Hospitalisations, Mortality	3.5 years median follow-up
	Singla [36] (abstract)	2016	74	[58]	57	Non-dialysis CKD 3-4	Identify prevalence and associations of low health literacy	Participants already recruited to a clinical trial in the Bronx, NY	38% non-Hispanic black, 8% non-Hispanic white, and 48% Hispanic	None stated	REALM	Hospitalisations Dialysis initiation.	24 months

	Study	Year	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Setting & recruitment method	Participants	Exclusion criteria	Health Literacy measure	Outcome variables tested	Follow-up time
Intervention pilot	Basu [14] (abstract)	2015	214	-	-	Non-dialysis and dialysis CKD	Pilot of education tool with pre-and post-intervention knowledge survey	3 kidney transplant centres	-	None stated	NVS	Improvement in Dialysis/transplant knowledge	Post-intervention
Cross-sectional studies	Adeseun [13]	2012	72	[52]	68	Incident Dialysis (HD or PD)	Examine relationship between HL and CV disease risk factors	Adults from transplant evaluation clinics	100% with LHL were Black, compared to 50% of those with Adequate HL	Previous coronary revascularisation, cardiac devices or weight >350lbs	STOFHLA	BP, lipid profile, waist-to-hip ratio, BMI, Tobacco use	-
	Blandon [15] (abstract)	2011	225	-	49	Non-dialysis CKD 2-4	HL and BP control in Hispanic Americans	Adults from nephrology outpatients clinic	91% Hispanic, 73% low income, 61% diabetic	None stated	STOFHLA (English or Spanish)	BP control	-
	Cavanaugh 3 [16] (abstract)	2010	50	[51]	48	Prevalent HD	Association of HL and type of dialysis access used	Adults from a single dialysis unit	74% Black, 33% dialysis catheter	None stated	REALM	Dialysis catheter use	-
	Dageforde [19]	2015	104	[53]	61	Dialysis (n=14) and non-dialysis CKD (n=90)	Characteristics of attenders vs absentees for kidney transplant evaluation appointments	Patients scheduled for initial evaluation for kidney transplant at a single centre	46% white	<18, Non-English speakers, cognitive impairment.	BHLS (0-15)	Attendance vs non-attendance	-
	Devraj [20]	2015	150	45% over 60	47	Non-dialysis CKD1-4	Relationship between HL and eGFR	Adults attending follow-up nephrology outpatient appointments at a single centre. Given a $20 merchandise card to participate	40% white, 41% Hispanic	<21, non-English speaking, AKI, cognitive impairment defined by medical notes, or if <4 on cognition screening test, Poor visual acuity	NVS	eGFR (MDRD formula), CKD stage, CKD self-management knowledge	-
	Foster [21]	2011	238	[58]	54	Prevalent Dialysis (HD or PD)	Assess disaster preparedness in dialysis patients	Adults approached during dialysis at 6 dialysis units	57% Black 6% Spanish-speaking, 94% English Speaking	<18, unable to understand consent process	STOFHLA	Disaster preparedness	-

	Study	Year	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Setting & recruitment method	Participants	Exclusion criteria	Health Literacy measure	Outcome variables tested	Follow-up time
Cross-sectional studies (continued)	Gordon [22]	2011	124	[47]	57	Transplant	Relationship between HL, transplant knowledge and graft function	Sequential transplant recipients from a single centre recruited at post-transplant clinic visit for 30-minute interview.		<18, Non-English-speaking; Visually impaired, Too unwell to participate	STOFHLA and REALM-T	Transplant function	-
	Grubbs [24]	2009	62	[52]	66	Prevalent HD	Association of poor HL with access to transplantation	Adults approached during dialysis session in 5 dialysis units.	73% Black	<18, >75, ethnicity other than Black or white, <9 months on dialysis, previous transplant, cognitive impairment	STOFHLA	Time from dialysis start to referral for tx evaluation, time from referral to listing (measured retrospectively)	-
	Jain [25] (abstract)	2005	92	63		Prevalent HD	Measure HL in prevalent HD patients. Assess relationship with demographics and quality measures	HD outpatients at 2 dialysis units	40% white	None stated	REALM	IDWG, Phos, Kt/V	-
	Jang [26] (abstract)	2014	110	>65 (exact figure not known)	58	Prevalent HD	Compare medication label understanding to REALM-SF	Adults from 3 dialysis centres	83% white. 11% hadn't completed high school	<18. Non-English speaking, 'unable to reasonably manage medications'	REALM-SF	Medication label understanding	-
	Kazely [27]	2014	127	[53]	48	Advanced CKD pre-dialysis or pre-transplant, dialysis or transplant	Develop and pilot a new tool for measuring HL in ESRD, specific to decision-making	Recruited from OP clinics.	Pre-transplant dialysis, transplant or planned vascular access procedure	Non-English speaking.	NVS and REALM-T	DMCAT decision-making tool	
	Nelson [29] (abstract)	2015	208	[72]	56	Non-dialysis CKD3b-5	Relationship between HL, medicines management capacity and treatment adherence	Adults under regular nephrology care in a single unit		None stated	REALM	Medicines management capacity. Self-reported medication adherence	
	Posadas [30] (abstract)	2011	83	-	43	Prevalent HD	Identify patient factors associated with dialysis catheter use	Single HD unit	-	None stated	STOFHLA	HD catheter use	-

	Study	Year	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Setting & recruitment method	Participants	Exclusion criteria	Health Literacy measure	Outcome variables tested	Follow-up time
Cross-sectional studies (continued)	Puher [31] (abstract)	2014	512	[66]	50	Non-dialysis CKD3-5	Assess relationship between HL and patient understanding	Nephrology outpatients surveyed on understanding of kidney tests via an online portal	97% white	<2 clinic attendances. Patients who don't use online portal.	BHLS (0-15)	Self-reported understanding of test results	-
	Rao [32] (abstract)	2016	52	-	-	Non-dialysis CKD4-5	Examine barriers to effective dietary adherence	English and Spanish speaking adults with CKD	-	Non -English or Spanish speakers	NVS	Intake of restricted nutrients. Knowledge of restricted foods.	-
	Segal [33] (abstract)	2016	108	[60]	56	Non-dialysis CKD1-5	Identify patient factors associated with poor CKD awareness	Adults from a university nephrology practice, convenience sample	67% white	None stated	REALM-SF	CKD awareness (by knowledge survey)	-
	Shirsalkar [34] (abstract)	2014	56	-	-	Prevalent HD	Identify patient factors associated with dialysis adherence and IDWG	-	Veterans	None stated	STOFHLA	IDWG, dialysis knowledge	-
	Singh [35] (abstract)	2012	101	-	49	Prevalent HD	Association of HL with dialysis quality measures	Adults in a single dialysis centre	-	None stated	STOFHLA	PTH, Phos, Alb, infections, hospitalisations, vascular access	-
	Vourakis [37] (abstract)	2012	122	[69]	54	Prevalent HD	Measure associations between HL and serum phosphate and albumin	Convenience sample from 3 urban HD facilities	22% Black	None stated	REALM-SF	Phos.	-
	Weng [38]	2013	252	[55]	60	Prevalent Transplant	Prevalence and correlates of medication non-adherence	Adults approached during a transplant clinic visit at a single centre. Offered $15	27% Black	<6 months post-transplant, <18, Non-English speakers, Unable to consent. Dual organ transplant.	STOFHLA	Medication non-adherence (survey measure)	-

	Study	Year	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Setting & recruitment method	Participants	Exclusion criteria	Health Literacy measure	Outcome variables tested	Follow-up time
	Wright [39]	2011	401	58	53	Non-dialysis CKD1-5	Measure awareness and knowledge of CKD to develop a CKD knowledge survey	Adults attending a follow-up nephrology clinic appointment at a single centre. Offered $10	83% white	<18, Non-English speakers, kidney transplant or dialysis, vision or cognitive impairment	REALM	Objective kidney disease knowledge	-
Cross-sectional studies (continued)	Wright-Nunes 1 [40]	2011	399 (all included in Wright)	[57]	53	Non-dialysis CKD1-5	Develop and validate a measure of perceived kidney disease knowledge	Adults at single centre asked to complete a survey (written or read aloud). Offered monetary compensation.	81% white, 78% CKD3-5.	<18, Non-English speakers, kidney transplant or dialysis, vision or cognitive impairment	REALM	Perceived kidney disease knowledge, patient satisfaction with clinician communication	-
	Wright-Nunes 2 [41]	2015	155	57	54	Non-dialysis CKD1-5	Measure knowledge of dietary sodium	Adults at single centre asked to complete a survey (written or read aloud). Offered monetary compensation.	78% white	<18, Non-English speakers, kidney transplant or dialysis, vision or cognitive impairment	REALM	Sodium knowledge	-

Table 4: Summary of tested associations between limited health literacy (or lower health literacy as a continuous measure) and outcomes in univariate models. Filled markers indicate statistically significant associations. Unfilled markers indicate non-significant associations. Shading of author name indicates cohort study. ED: Emergency department; BP: Blood pressure; IDWG: Intra-dialytic weight gain; HDL: High-density lipoprotein; LDL: Low-density lipoprotein. *In a subgroup only (women with diabetes), not significant for other groups.

Group	Author	Medication non-adherence	Lower medicines management capacity	Medicaiton adherence score	CKD awareness	Lower objective kidney disease knowledge	Lower percieved kidney disease knowledge	Poorer understanding of test results	Understanding of medication label	Dietary knowledge	CKD knowledge improvement after education	CKD self-management score	Prefer kidney transplant/certainty of decision	Lower transplant decision-making capacity	Satisfaction with clinician communication	Disaster preparedness	Hospitalisation rate	ESRD-related hospitalisations	ED visits	Missed dialysis sessions	Abbreviated dialysis sessions	Shorter time to dialysis start	Systolic BP	Higher Diastolic BP	Higher Mean arterial pressure	Poorer BP control	Dietary intake of sodium, phosphate etc.	Catheter use (compared to fistula)	Fistula (compared to catheter)	Body mass index	Waist-hip ratio	Lower dry weight	IDWG	Attendance at transplant assessment clinic	Lower eGFR	CKD stage	Haemoglobin	Transferrin saturation	Kt/V	Albumin	Lower Phosphate	Calcium	Calcium-Phosphate product	Intact Parathyroid hormone	HDL	LDL	Triglycerides	Time from dialysis start to transplant referral	Increased time to transplant wait-listing	Increased Mortality
Non-dialysis CKD	Basu										•																																							
	Blandon																									•*																								
	Dageforde																																	o																
	Devraj												o																						•	o														
	Kazley														•																																			
	Nelson		•	o																																														
	Puher								•																																									
	Rao							o																				o																						
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	Jain																														o										o	o								
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Trans-plant	Gordon																																		o															
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	Weng	o																																																

Table 5: Summary of tested associations between limited health literacy (or lower health literacy as a continuous measure) and outcomes in multivariate models, with covariates included in each model. Filled markers indicate statistically significant associations. Unfilled markers indicate non-significant associations. Shading of author name indicates cohort study. ED: Emergency Department; BP: Blood pressure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Hb: Haemoglobin; Phos: Phosphate; iPTH: Intact parathyroid hormone;

Outcomes (● = statistically significant; ○ = non-significant)

Group	Study	Model	Lower objective kidney disease knowledge	Lower percieved kidney disease knowledge	Understanding of test results	Hospitalisation rate	ESRD-related hospitalisations	Missed dialysis sessions	ED visits	Systolic BP	Higher Diastolic BP	Higher Mean Arterial Pressure	Body mass index	Waist-hip ratio	Catheter use (compared to fistula)	Lower dry weight	Lower eGFR	Triglycerides	HDL	LDL	Atherosclerotic event	Progression to ESRD	Increased time to transplant referral	Increased time to transplant wait-listing	Transplantation	Change in Kt/V, Hb, Phos or iPTH over 9 months	Transplant function	Increased Mortality
Non-dialysis CKD	Devraj																●											
	Lora					●															●	○						○
	Puher				●																							
	Wright		●																									
	Wright-Nunes 1			●																								
Dialysis	Adeseun									○	●	●	○	○				○	○	○								
	Cavanaugh 1	1													○													●
		2																								○		
	Cavanaugh 2																											●
	Cavanaugh 3															●												
	Green						●	●	●																○			○
	Grubbs																						●	○				
Transplant	Gordon																										○	

Covariates (▓ = covariate included in model)

Group	Study	Model	Age	Age at dialysis start	Gender	Ethnicity	Smoking	Country of residence	Income	Education	Health insurance type	Employment	Diabetes	Overall comorbidity	Kidney disease duration	Blood Pressure	Proteinuria	ACEi/ARB use	Body mass index	HbA1c	Transplant date/donor/previous transplants	eGFR	Dialysis vintage	Dialysis schedule/vascular access	"Lab values"	Dialysis unit	Randomisation group within study	Support person	Participation in kidney education class	Know someone with CKD	Aware of CKD diagnosis	Doctor visits	Use of educational resources
Non-dialysis CKD	Devraj		▓		▓	▓				▓			▓																				
	Lora		▓	▓	▓	▓	▓		▓	▓			▓	▓	▓	▓	▓	▓	▓	▓	▓	▓											
	Puher		▓		▓	▓			▓	▓			▓																	▓			▓
	Wright		▓		▓	▓																							▓		▓		
	Wright-Nunes 1		▓		▓	▓																							▓			▓	
Dialysis	Adeseun		▓		▓	▓							▓																				
	Cavanaugh 1	1	▓		▓	▓				▓				▓																			
		2	▓		▓	▓				▓				▓																			
	Cavanaugh 2		▓		▓	▓				▓																	▓						
	Cavanaugh 3		▓		▓																		▓										
	Green		▓	▓	▓	▓				▓			▓											▓		▓							
	Grubbs		▓		▓	▓							▓																			▓	
Transplant	Gordon		▓																		▓												

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Legends to figures

Figure 1: Study identification process.

Citations for the 25 studies which were fully reviewed, but not included are shown in the Supplementary material.

CINAHL: Cumulative Index to Nursing and Allied Health Literature; ASN: American Society of Nephrology Kidney Week; ERA-EDTA: European Renal Association-European Dialysis and Transplant Association Congress.

Figure 2: Summary of effect sizes for associations with limited (vs adequate) health literacy in cohort studies.

Covariates included in multivariate models are shown in Table 5. Cross-sectional results from baseline data in cohort studies not shown (shown in Tables 4 and 5). Results from Singla et al. [36] (a negative association between limited health literacy and hospitalisations, and a positive association between limited health literacy and dialysis initiation) are not shown because measures of effect were not available.

ESRD: End-Stage Renal Disease; HR: Hazard Ratio; RR: Rate Ratio; ED: Emergency Department;