UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

Primary Care and Population Sciences

HEALTH LITERACY AND ITS RELATIONSHIP WITH PROCESS AND OUTCOMES IN ADVANCED KIDNEY DISEASE

by

Dr Dominic M Taylor Mb ChB MRCP (UK)

Thesis for the degree of Doctor of Medicine

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ABSTRACT

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Introduction: Management of Chronic Kidney Disease (CKD) aims to reduce the risk of kidney failure and cardiovascular disease and, if appropriate, prepare patients for renal replacement therapy: dialysis or kidney transplantation. Kidney transplantation is superior to dialysis in terms of survival and quality of life, but donor organs are a limited resource. CKD care pathways are complex, and shared decision-making and self-care activities are promoted. Health literacy is an attribute facilitating access, understanding, appraisal and use of health-related information. Socioeconomic disparities exist in CKD care and outcomes. Low health literacy is associated with both low socioeconomic status (SES) and poorer health outcomes, so is hypothesised to mediate pathways which promote health inequity.

Aims/Methods: This thesis investigates:

- The prevalence of limited health literacy at different treatment stages of CKD, and associations with demographics and SES (systematic review and meta-analysis).
- Associations between low health literacy and CKD outcomes (systematic review)
- The prevalence and associations of limited health literacy in UK patients with advanced CKD in the Access to Transplant and Transplant Outcome Measures (ATTOM) study
- Associations between limited health literacy and clinical outcomes, including deceased- and living-donor kidney transplantation, using prospective data from the ATTOM study.
- Health literacy as a mediator in the relationship between low educational level and time to transplant wait-listing and deceased- or living-donor kidney transplantation

Results: The pooled prevalence of limited health literacy among people with CKD was 25%. Prevalence was lower among transplanted patients compared to those with non-dialysis or dialysis CKD. Limited health literacy was consistently, independently associated with low SES and non-white ethnicity. Current evidence from peer-reviewed literature for associations between low health literacy and clinical outcomes was limited. In the ATTOM study, limited health literacy was independently associated with low socioeconomic status and increased comorbidity. Prevalence of limited health literacy was significantly lower among transplant recipients compared to dialysis or wait-listed patients, after adjustment for comorbidity. Limited health literacy was associated with reduced chance of transplant wait-listing, living-donor transplant or transplantation from any donor at 2 years from dialysis start. In mediation analysis, health literacy mediated 25-30% of the total effect of low educational level on increased time to deceased-donor transplant wait-listing, living-donor transplantation or transplantation from any donor type.

Conclusions: A quarter or more of patients with CKD have limited health literacy, so are unlikely to be able to fully understand or appraise health-related information or navigate care pathways if standard communication methods are used. By mediating the relationship between low socioeconomic status and access to transplantation, health literacy differences may promote inequity. Interventions which successfully reduce these effects could improve patients' understanding, reduce inequity and improve outcomes.

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DECLARATION OF AUTHORSHIP

I, **Dominic M Taylor** declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

Health literacy and its relationship with process and outcomes in advanced kidney disease

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Work from this thesis has been presented, published or prepared for publication as:

   Papers

   - **Taylor DM**, Bradley JA, Bradley C, Draper H, Johnson R, Metcalfe W, Oniscu G, Robb M, Tomson C, Watson C, Ravanan R and Roderick P (2016). *Limited health literacy in advanced kidney disease.* Kidney International **90**(3): 685-695. PMID: 27521115
   - **Taylor DM**, Fraser SDS, Bradley JA, Bradley C, Draper H, Metcalfe W, Oniscu GC, Tomson CRV, Ravanan R and Roderick PJ (2017) *A Systematic Review of the Prevalence and Associations of Limited Health Literacy in CKD.* Clinical Journal of the American Society of Nephrology 12(7):1070-1084 PMID: 28487346
   - **Taylor DM**, Fraser SDS, Oniscu GC, Tomson C, Ravanan R and Roderick P. *Health literacy and patient outcomes in chronic kidney disease: a systematic review* Nephrology, Dialysis, Transplantation (under review July 2017)

   Oral conference presentations

   - **D M Taylor** on behalf of the ATTOM investigators. *Patients selected for Kidney Transplantation have higher Health Literacy: Results from the ATTOM Study* British Transplant Society Annual Congress. February 2016 (Abstract presentation)
   - **D M Taylor** on behalf of the ATTOM investigators. *A Large-scale, UK-wide Analysis Of Health Literacy In ESRD: Results From The ATTOM Study.* UK Kidney Week: Joint

conference of the British Renal Society and UK Renal Association. June 2016 (Abstract presentation)

- **D M Taylor** on behalf of the ATTOM investigators. *Limited health literacy in advanced kidney disease: Prevalence, associations and outcomes* British Renal Society, Nottingham April 2017 (Invited session)

Poster Presentations

- **D M Taylor** on behalf of the ATTOM investigators. *Low Socioeconomic Status and Co-Morbidity Are Associated with Limited Health Literacy in RRT Patients – Results from the ATTOM Study.* American Society of Nephrology Kidney Week. November 2015
- **D M Taylor** on behalf of the ATTOM investigators. *Does health literacy explain differences in patterns of care by socioeconomic status among dialysis patients?* UK Kidney Week (UK Renal Association) Liverpool UK, June 2017

Signed:

Date:

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Lastly, I wish to thank my wife, Frances and my daughter, Florence for their understanding, encouragement, tea, and advice on when to finish working for the day.

Abbreviations

The following abbreviations are used in the main text of this thesis. Any abbreviations used only in tables are defined in the table legends.

ACR	Albumin: Creatinine Ratio
ADPKD	Autosomal-Dominant Polycystic Kidney Disease
AFT	Accelerated Failure Time (Survival Modelling)
AKI	Acute Kidney Injury
(a)APD	(assisted) Automated Peritoneal Dialysis
ATTOM	Access to Transplant and Transplant Outcome Measures (study)
BHLS	Brief Health Literacy Screen
CAPD	Continuous Ambulatory Peritoneal Dialysis
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease-Epidemiological Collaboration (eGFR equation)
CKD-MBD	Chronic Kidney Disease-Mineral Bone Disorder
DBD	Donor after Brain Death
DCD	Donor after Cardiac Death
ECD	Extended Criteria Donor
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESKD	End-Stage Kidney Disease
ESRD	End-Stage Renal Disease
(e)GFR	(estimated) Glomerular Filtration Rate
GN	Glomerulonephritis
HD	Haemodialysis
HDF	Haemodiafiltration
HLA	Human Leucocyte Antigen
HLS-EU	Health Literacy Survey-European Union
ICE	Imputation by Chained Equations
IMD	Index of Multiple Deprivation
iPTH	Intact Parathroid Hormone
IQR	Interquartile Range
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LKD	Living Kidney Donor
MAR	(data) Missing At Random

Abbreviations

MDRD	Modification of Diet in Renal Disease (eGFR equation)
NHS	(UK) National Health Service
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Clinical Excellence
NVS	Newest Vital Sign
OR	Odds Ratio
PD	Peritoneal Dialysis
PRD	Primary Renal Diagnosis
PROSPERO	PROSPEctive Register Of systematic reviews
QOF	Quality Outcomes Framework
RCT	Randomised, Controlled Trial
REALM	Rapid Estimate of Adult Literacy in Medicine
REALM-SF	Rapid Estimate of Adult Literacy in Medicine-Short Form
REALM-T	Rapid Estimate of Adult Literacy in Medicine-Transplant
RRT	Renal Replacement Therapy
SD	Standard Deviation
SDM	Shared Decision-Making
SEM	Structural Equation Modelling
SES	Socioeconomic Status
SILS	Single-Item Literacy Screener
SLE	Systemic Lupus Erythematosus
SPK	Simultaneous Pancreas-Kidney (Transplant)
STOFHLA	Short Test of Functional Health Literacy in Adults
TILS	Two-Item Literacy Screener
TIN	Tubulointerstitial Nephritis
TOFHLA	Test Of Functional Health Literacy in Adults
UKRR	UK Renal Registry
ULN	Upper Limit of Normal
URR	Urea Reduction Ratio

Introduction and thesis aims

Chronic kidney disease (CKD) is common, and is associated with significant morbidity and mortality, predominantly through associated cardiovascular disease.[1] Progression of CKD increases cardiovascular risk[2] and the risk of kidney failure.[3] Clinical management of CKD aims to reduce these risks, and where appropriate, prepare people with impending kidney failure for renal replacement therapy: dialysis or a kidney transplant. For patients well enough to receive a kidney transplant, this offers advantages over dialysis in terms of quality and quantity of life.[4, 5] However, a kidney transplant is not immediately available to all who need it, in part because of a shortage of deceased-donor organs and limited capacity for living donation. Treatment in CKD involves multiple episodes of contact with clinicians, and exposure to often complex written materials relating to CKD and its treatment. Healthcare policy promotes self-care and shared decision-making activities[6, 7] with the aim of improving patient engagement and delivering care which meets the needs of the patient. However, adequate understanding of disease and treatment is a prerequisite for involvement in these activities.

Although the majority of healthcare services in the UK are free at the point of use, there remains significant variation in individuals' health outcomes. A degree of this variation is related to social determinants of health, including socioeconomic status (SES). In UK patients with CKD, low SES is associated with increased mortality in people with CKD[8] and reduced access to kidney transplantation.[9, 10] SES differences are hypothesised to promote health inequity via multiple mechanisms.[11] Many of these mechanisms (for instance, the effects of environmental exposures) do not take effect at the point of healthcare delivery, so may not be of direct concern to those designing clinical healthcare services. However, one factor that could influence effective treatment delivery is patients' level of 'health literacy'. First described in the 1970s, 'health literacy' has been defined as:

'people's knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning being ill, being at risk and staying healthy, to maintain or improve quality of life during the life course.'[12]

As such, low health literacy could reduce the effectiveness of individuals' interactions with healthcare services, reducing their level of understanding. People with lower health literacy may lack the skills necessary to engage with self-care and shared decision-making activities. Low health literacy has established links to low SES, so health literacy has been implicated as a potential mediator in the association between low SES and poor health outcomes.[13] Strategies to improve health literacy or reduce the effects of low health literacy on outcomes have been developed in many healthcare settings.[14] However, knowledge of health literacy applicable to UK patients with CKD is lacking. The majority of health literacy research originates from the USA,[15, 16] where relationships between SES, ethnicity and health are vastly different from the UK for societal reasons.[17] Even within CKD populations in the USA, it has not been clearly established how many patients with CKD are affected by poor health literacy,[18] and evidence for clear associations with socioeconomic factors, demographics and outcomes in CKD populations is incomplete. Without further knowledge of the mechanisms by which poor health literacy could negatively affect patients with CKD, interventions aiming to reduce health literacy-related inequity cannot be appropriately targeted, may not be effective, and their funding cannot be easily justified.[19]

The aims of this thesis are:

- To describe the prevalence of low (‘limited’) health literacy among patients with CKD, and to identify differences in health literacy between patients at different stages of disease and treatment
- To identify associations between health literacy and clinical outcomes among patients with CKD, including access to transplantation
- To investigate for a mediating effect of health literacy in the relationship between low SES and outcomes in CKD

These aims are addressed through:

- Systematic review and meta-analysis of literature to establish the prevalence of limited health literacy and its associations with patient characteristics and outcomes in **Chapter 3**
- Novel investigation of health literacy in a large UK cohort of patients with advanced CKD within the Access to Transplant and Transplant Outcome Measures (ATTOM) study in **Chapters 4, 5, and 6**

Chapters 1 and 2 provide background information on CKD, SES and health literacy, and the context for investigation of the effects of health literacy on CKD care in subsequent chapters. The final chapter **(Chapter 7)** discusses the findings of this thesis.

Chapter 1: Introduction to chronic kidney disease

This chapter describes the structure and function of the kidneys in order to allow an understanding of the pathology, treatment and epidemiology of Chronic Kidney Disease (CKD). The ‘patient pathways’ of treatment of CKD, and the concepts of self-care and shared decision-making are described, providing context for discussion of the potential effects of patient factors such as socioeconomic status (SES) and health literacy in Chapter 2.

1.1 Structure and function of the kidneys

Describing the structure and function of the kidneys[20, 21] in this section allows clear explanation of kidney *dysfunction* in section 1.2.

The kidneys are solid abdominal organs. They have several critical functions:

- Excretion of the waste products of metabolism
- Control of the electrolyte and water composition of extracellular fluid (homeostasis);
- Endocrine (hormone-driven) functions, which include production of red blood cells (erythropoiesis), bone-mineral metabolism and blood pressure control.

1.1.1 Blood supply

The kidneys are usually supplied with blood via a single artery and vein. Blood enters the kidney via the renal artery and passes via smaller arteries to the glomerulus. The glomerulus is an arrangement of semi-permeable capillaries, which act as a filter. Water and electrolytes (filtrate) from the glomerulus passes into the nephron via the glomerular capsule (Figure 1-1). From the glomerulus, blood flows to the efferent arteriole, and then to the peritubular capillaries, which pass adjacent to the renal tubules before draining into the venous system.

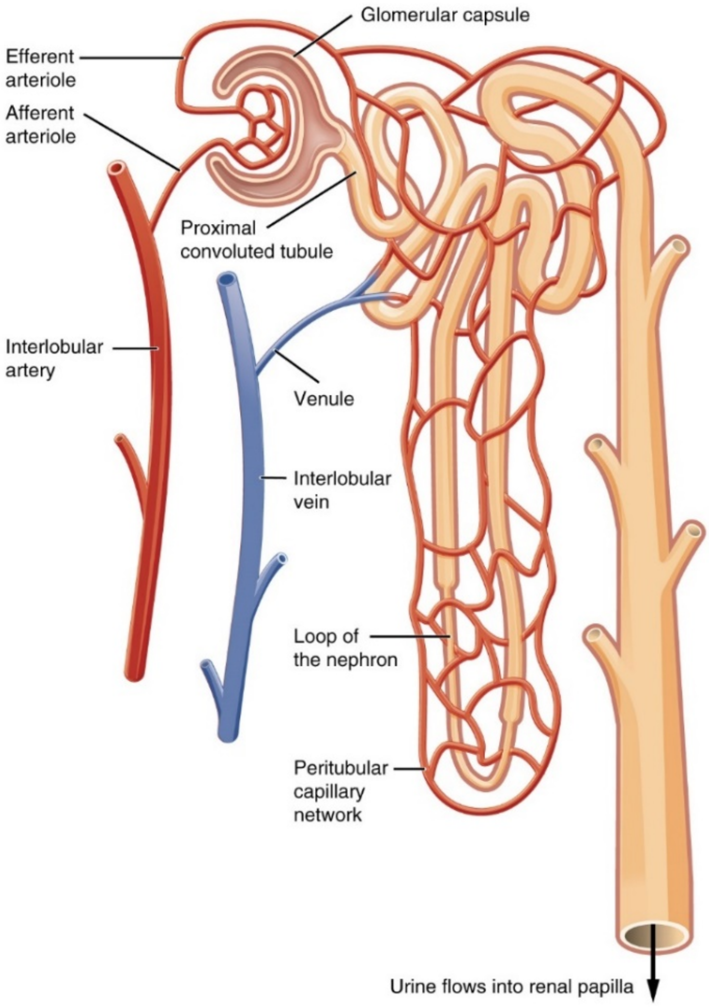


Figure 1-1: The glomerulus and its blood supply[22]

1.1.2 Nitrogenous waste and water excretion

Each kidney contains 1-1.5 million nephrons. The nephron is a microscopic tube, which collects the filtrate from the glomerulus. (Figure 1-1). Filtrate flows from here to the renal tubule, which is formed of the proximal tubule, loop of Henle, distal tubule and collecting duct, each having a distinct function in maintaining water and electrolyte balance by controlling absorption or secretion of solute or water from the nephron to the peritubular capillaries. Filtrate drains from the collecting duct to the renal calyx, after which it is referred to as urine. Urine drains from renal calyx into the ureter and bladder, from where it is expelled by micturition.

The excretion of water and electrolytes by the kidneys is tightly controlled in order to maintain the optimal electrolyte concentrations in the body’s extracellular fluid for cells to function. This process is part of body homeostasis, without which heart, muscle and brain dysfunction occurs.

1.1.3 Endocrine functions of the kidneys

The kidneys also have important endocrine functions:

They are the principal organs producing the hormone erythropoietin. Erythropoietin is produced in response to reduced oxygen delivery to the kidney. Its effect is to stimulate bone marrow cells to produce erythrocytes: oxygen-carrying red blood cells.

The kidneys perform another endocrine function by metabolism of vitamin D (cholecalciferol). Cholecalciferol is absorbed from food or synthesised in the skin via the action of ultraviolet light. Cholecalciferol itself is not active until metabolised to 25-hydroxy-cholecalciferol in the liver and then to 1-25-hydroxy-cholecalciferol in the kidney by the enzyme 1-α-hydroxylase, produced in the renal tubule. This ‘activated’ vitamin D promotes calcium absorption in the gut, and reabsorption of calcium from the filtrate in the renal tubule. This process is part of the complex mechanism of calcium homeostasis, which maintains the environment necessary for cellular function, and is interlinked with processes for maintaining bone health.

Lastly, the kidneys play a role in maintaining blood pressure. In response to reduced kidney blood flow, the hormone renin is produced. Renin release controls the renin-aldosterone-angiotensin system, a hormonal pathway which acts to increase salt and water retention and therefore increase blood pressure.

Table 1-1 summarises the functions of the kidneys.

Table 1-1: Summary of the functions of the kidneys

Excretory/homeostatic	Endocrine
• Maintenance of extracellular fluid composition by water and electrolyte homeostasis • Excretion of nitrogenous waste • Metabolism of drugs	• Control of erythrocyte production in response to hypoxia via erythropoietin production • Control of calcium homeostasis by metabolism of vitamin D • Control of blood pressure via the renin-aldosterone-angiotensin system

1.2 Chronic Kidney Disease classification, progression and epidemiology

1.2.1 Measurement of excretory kidney function

The several functions of the kidneys cannot be reflected in a single measure. However, the most immediate and life-threatening consequences of loss of kidney function are those which result from the loss of the ability to excrete waste and regulate water and electrolyte balance. As such, the level of *excretory kidney function*, which describes kidneys' efficiency in performing these functions, is the most common marker used to describe kidney disease severity and is used in CKD classification (Section 1.2.4). It is quantified by Glomerular Filtration Rate (GFR): the volume of blood filtered at the glomerulus per unit time (expressed in millilitres per minute, ml/min).

To measure GFR accurately, a substance which is filtered at the glomerulus, and neither absorbed nor secreted in the renal tubule could be measured in the blood and urine during a unit of time. From this, the rate of excretion of this substance and hence GFR could be calculated. However, no such substance is known to exist. The most *accurate* available tests of kidney function involve the infusion of exogenous substances close to meeting these criteria (eg: inulin, a fructose polymer) but these are too time-consuming or invasive for routine use. Instead, measurement of serum creatinine has become the most commonly used measure of excretory kidney function. Creatinine is a substance produced from skeletal muscle. It does not satisfy the above criteria completely: its rate of production is not constant and may vary with dietary changes (it is present in dietary meat) and it is secreted in the renal tubule as well as being filtered at the glomerulus. Despite these imperfections, serum creatinine is easy to measure by a single blood test, hence its widespread use.

The rate of creatinine production in an individual depends on muscle mass, so the level of serum creatinine which indicates a specific GFR varies between individuals: a serum creatinine level which represents normal kidney function for a very muscular person may indicate severe kidney disease for someone with low muscle mass. To account for this, and to make estimates of kidney function easier to interpret, equations have been produced based on experimental work where serum creatinine measurements were compared to the results of reference GFR measurements using more accurate methods. The equations most commonly used in current practice are the 'Modification of Diet in Renal Disease' (MDRD) and 'Chronic Kidney Disease- Epidemiology Collaboration' (CKD-EPI) formulae.[23, 24] Both use age, gender and ethnicity as estimators of body muscle mass to produce an estimated GFR ('eGFR'). The 2006 National Service Framework for Renal services specified that $\mathrm{eGFR}_{\mathrm{Creatinine}}$ calculations should be reported alongside serum creatinine measures in UK clinical biochemistry laboratories.[25] The KDIGO Clinical Practice Guideline for Evaluation and Management of CKD (2012)[26] and subsequently the NICE guideline on CKD (2014)[27] recommended routine use of the CKD-EPI equation to calculate $eGFR_{Creatinine}$ because of superior accuracy compared to the MDRD equation. Both equations produce GFR estimates adjusted for body surface area, and therefore in the unit 'ml/min/1.73m^2'.

Cystatin C is an endogenous protein whose measurement can be used to estimate GFR. Its production is not related to muscle mass, so it has utility in situations where $eGFR_{Creatinine}$ is likely to be less accurate, such as among individuals at extremes of muscle mass.[28] It has been approved for use to estimate kidney function for several years but its use in clinical practice has been limited by lack of consensus on the optimal method of calculating $eGFR_{CystatinC}$. Cystatin C measurement is now recommended in addition to creatinine measurement to confirm the presence or absence of CKD in some situations (Section 1.2.4).[29]

1.2.2 Proteinuria and albuminuria

An important marker of kidney damage is the presence of protein (or a specific protein, albumin) in the urine. In health, only small amounts of protein (<200mg/24 hours) cross the glomerular basement membrane and are excreted in urine. Many kidney diseases result in glomerular inflammation and fibrosis, which leads to proteinuria (or albuminuria), proportional to the extent of glomerular inflammation. The level of proteinuria is therefore predictive of the rate of future GFR loss ('progression').[30, 31] In early CKD, especially in patients with diabetic nephropathy, total protein excretion may lie within the normal range, yet albuminuria may be increased. Even low-level albuminuria (30-300mg/24 hours, 'microalbuminuria') is associated with a significant increase in risk of CKD progression and cardiovascular risk.[32] Measurement of albuminuria by a laboratory urine test (urine albumin: creatinine ratio, uACR) now forms part of the CKD classification system (Section 1.2.4).

1.2.3 Other kidney functions

The endocrine functions of the kidney (Section 1.1.3) can become impaired in people with progressive CKD, leading to anaemia and impaired bone metabolism. These consequences of kidney disease occur at predictable levels of impairment in excretory kidney function and require specific treatment, but are not used in CKD classification. In people receiving dialysis, adequate correction of these parameters is used as a marker of quality of dialysis care. (Section 1.3.2.3)

1.2.4 CKD definition and classification

CKD is defined by 'Kidney Disease-Improving Global Outcomes' (KDIGO) as 'abnormalities of kidney structure or function, present for more than 3 months, with implications for health.'[26] Current UK guidance from the National Institute for Health and Care Excellence (NICE, 2014)[27] draws on previous guidelines from 'Kidney disease: Improving Global Outcomes' (KDIGO,2012)[26], and the National Kidney Foundation: Kidney Disease Outcomes Quality Initiative (KDOQI, 2002)[29] to define and risk-stratify CKD. By these criteria, a diagnosis of CKD can be made when an abnormality in kidney structure or function is present for more than 3 months, including those with two $eGFR_{Creatinine}$ measurements less than $60ml/min/1.73m^2$ at a 90-day interval or greater, or with a higher $eGFR_{Creatinine}$ but with other abnormalities of kidney structure or function. Individuals with an $eGFR_{Creatinine}$ of $45\text{-}59ml/min/1.73m^2$ sustained for 90 days without other abnormality of kidney structure or function are now recommended to have an $eGFR_{CystatinC}$ test. In those with $eGFR_{CystatinC}$ above $60ml/min/1.73m^2$, the diagnosis of CKD should not be made, because Cystatin C more accurately predicts outcomes in this situation. Criteria for CKD diagnosis are listed in Table 1-2.

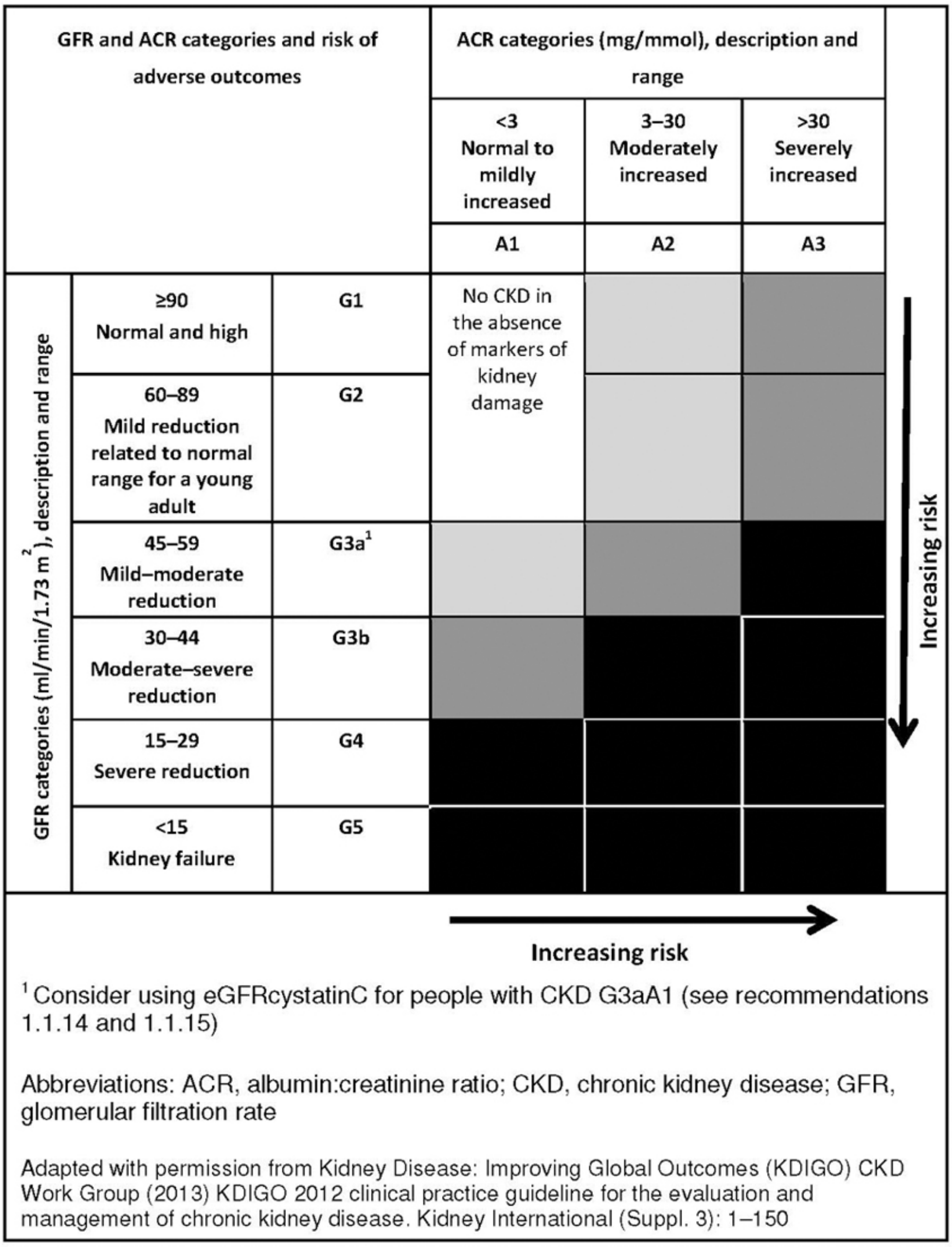
Table 1-2: CKD definition by abnormality of structure and function

From KDIGO 2012 Clinical practice guidelines for Evaluation and Management of Chronic Kidney Disease[26]

Criteria for CKD diagnosis (either of the following present for >3 months)	
Markers of kidney damage (one or more)	Albuminuria (ACR >_3mg/mmol) Urine sediment abnormalities Electrolyte or other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	eGFR <60ml/min/1.73m2 (CKD stages G3a-G5)

KDIGO and NICE guidance recommends that albumin: creatinine ratio is used to define 'ACR categories' which are combined with 'GFR categories' to classify CKD, as shown in Figure 1-2.

Ascending GFR and ACR categories indicate increased cardiovascular risk (Section 1.2.7), and increased risk of worsening of kidney function (‘progression’) to the point of End-Stage Renal Disease (ESRD, which implies that renal replacement therapy may be indicated). Before this system was proposed, the six ‘GFR categories’ (1, 2, 3a, 3b, 4, 5) were used alone to classify CKD and were referred to as ‘CKD stages’, and this terminology is often still used in clinical and research practice.



GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
GFR categories (ml/min/1.73 m^2), description and range	≥90 Normal and high	G1	No CKD in the absence of markers of kidney damage	░	▒
	60–89 Mild reduction related to normal range for a young adult	G2		░	▒
	45–59 Mild–moderate reduction	G3a[1]	░	▒	█
	30–44 Moderate–severe reduction	G3b	▒	█	█
	15–29 Severe reduction	G4	█	█	█
	<15 Kidney failure	G5	█	█	█

Increasing risk

Increasing risk

[1] Consider using eGFRcystatinC for people with CKD G3aA1 (see recommendations 1.1.14 and 1.1.15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

Figure 1-2: **Classification of CKD by eGFR and level of albuminuria**

From KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[26]

1.2.5 Primary renal disease (PRD) and mechanisms of CKD progression

The primary pathology thought to have caused an individual to develop CKD is referred to as 'Primary Renal Disease' (PRD). Common PRDs in the UK include Glomerulonephritis (GN), Pyelonephritis (PN) or Tubulointerstitial Nephritis (TIN), diabetes, renovascular disease, hypertension, Autosomal-Dominant Polycystic Kidney Disease (ADPKD) and urological diseases.[33] Standardisation of PRD terms and definitions has been developed in the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) PRD coding system.[34] For 16% of UK patients starting RRT, PRD remains unknown. Definitive diagnosis, which requires kidney biopsy, is only obtained in clinical practice when the risk of performing the biopsy (bleeding) is outweighed by the benefits of diagnosis, for instance in cases of suspected glomerulonephritis requiring immunosuppressive treatment.[20] For this reason, many PRDs are defined by the clinical 'picture' of likely disease aetiology and not by biopsy.

By definition, an individual's PRD initiates CKD, but progression of CKD is thought to result from multiple interconnected disease processes, which may be unrelated to the PRD. Many patients will have CKD related to multiple pathologies, for instance coexisting diabetes, vascular disease and hypertension, where the development of hypertension and vascular disease are made more likely by diabetes. Although hypertension alone may cause kidney damage and the development of CKD, kidney dysfunction itself impairs salt and water excretion, leading to hypertension and further kidney damage. Positive feedback loops such as these can contribute to accelerated 'progression' of CKD (Figure 1-3).[35] Episodes of 'Acute Kidney Injury' (AKI) also contribute to the risk of CKD progression. AKI is an abrupt decline in kidney function (over less than 48 hours) often occurring during an acute illness.[36] AKI is associated with increased risk of CKD, ESRD and mortality.[37] Risk of AKI is increased by comorbidity (especially diabetes or congestive cardiac failure),[38] so the risk of AKI is likely to increase as CKD progresses (and comorbidity increases): a positive feedback loop similar to those described above.

Depending on PRD, the presence or absence of risk factors promoting CKD progression, episodes of AKI, and provision of disease- or risk-modifying treatment, CKD follows a variable clinical course. Where multiple risk factors for progression are present, rapid progression to ESRD is more likely, whereas when risk factors are successfully managed, impaired but stable kidney function may persist without progression. Symptoms specific to CKD ('uraemic symptoms') are often absent until CKD is relatively advanced (GFR category G4-5). Early symptoms can also be non-specific (eg: lethargy), so may not easily be identifiable as related to kidney dysfunction.

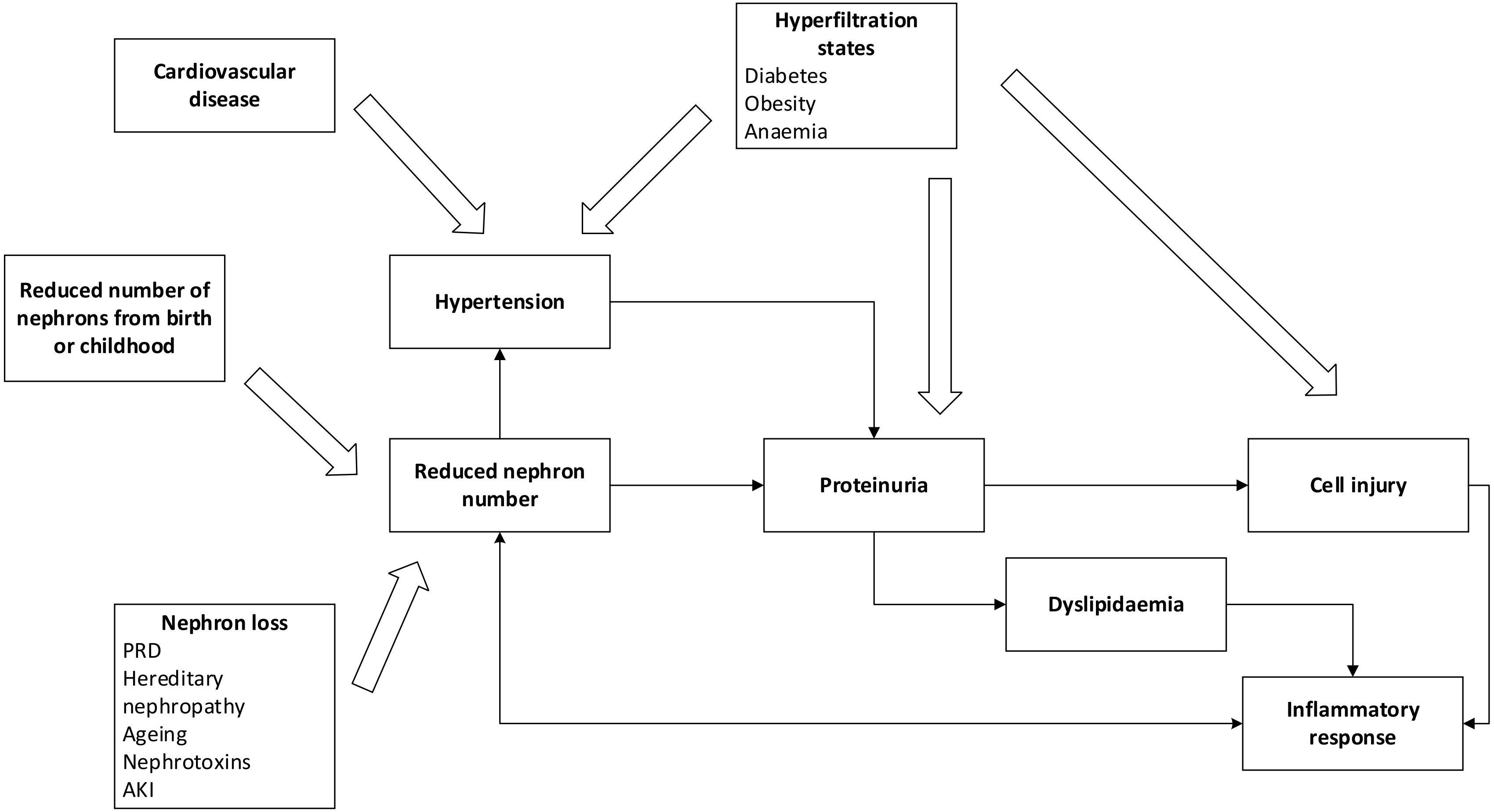


Figure 1-3: **Factors influencing CKD progression, adapted from Taal and Brenner 2006[35]**

PRD: Primary Renal Diagnosis; AKI: Acute Kidney Injury

1.2.6 CKD Epidemiology

Estimating the incidence of CKD in populations is not feasible because CKD often remains asymptomatic and undiagnosed until it reaches an advanced stage. Estimating the population prevalence of CKD based on all the criteria in Table 1-2 is also problematic (for instance, the majority of the population have not been screened for structural abnormalities of the renal tract). Instead, many studies of adult populations have used surrogate definitions of CKD defined by eGFR. Using this method, there is significant heterogeneity in reported CKD prevalence internationally: one systematic review found CKD prevalence estimates between 0.6% and 42.6% from 43 studies.[39] Although differing methods of GFR estimation and demographics of study samples in individual studies contribute to this heterogeneity,[40] genuine variation CKD prevalence is thought to exist between countries, even within Europe, attributed to differences in cultural lifestyle factors (diet, smoking), public health policy, genetics, and ethnicity.[41]

The 2009-10 Health Survey for England reported a prevalence of CKD (defined as eGFR<60ml/min/1.73m^2 by CKD-EPI formula) of 5.2%.[42] Factors associated with increased risk of CKD included increased age, female sex, lower SES (Section 2.1.2) smoking, obesity, diabetes and hypertension. In UK adults over 75, the prevalence of CKD as defined by eGFR<60ml/min/1.73m^2 is estimated at 56.1%,[43] though there is some debate as to the benefits (or potential harms[44]) of CKD diagnosis in this group. CKD diagnosis is associated with a significant increase in the absolute risk of death in older people, but the increase in relative risk is less marked.[45] Notably, the prevalence of self-reported, doctor-diagnosed CKD is far lower than the prevalence derived from eGFR,[46] likely to be explained by a large proportion of people with 'known' impaired GFR who aren't aware of a diagnosis of CKD. CKD unawareness is associated with older age, lack of educational qualifications and less advanced disease.[47] Individuals with CKD whose kidney function has never been measured are not accounted for in these prevalence estimates.

Although CKD is common, relatively few people appear to reach the point of requiring Renal Replacement Therapy (RRT: Dialysis or transplantation). In the UK in 2014, 115 per million population (pmp) started RRT.[48] In the same year, the prevalence of UK adult patients receiving RRT was 888 pmp.[49] Of course, these data exclude individuals with undetected ESRD or those with diagnosed ESRD who opt for conservative care (Section 1.3.2).

Diagnosis of CKD and RRT provision varies by ethnicity. People of South Asian or black ethnicity appear to have lower prevalence of early CKD, yet rates of renal replacement therapy provision in these groups are higher than in white populations. This may reflect differences in the rates of early detection of CKD between ethnic groups, increased rate of CKD progression, and reduced competing risk of morbidity and mortality compared to the white CKD population. [2, 48-51]

1.2.7 CKD and cardiovascular risk

CKD is associated with increased risk of cardiovascular morbidity and mortality, which increases as GFR reduces and with maximum risk for those with ESRD.[52] A 2004 cohort of 1.1 million adults reported progressive increases in the hazard ratio for cardiovascular events and mortality with increasing CKD stage in fully adjusted analyses.[2] Hazard ratio of any cardiovascular event was 3.4 (95% CI: 3.1-3.8) for patients with ESRD compared to those with normal kidney function. The hazard ratio for all-cause mortality was 5.9 (95% CI: 5.4-6.5). Albuminuria has an additive effect in further increasing this risk.[32, 53] Hypothesised causative mechanisms explaining the association between CKD and cardiovascular disease include increased levels of inflammation, anaemia, left ventricular hypertrophy, vascular calcification and endothelial dysfunction.

1.3 Medical management of CKD

1.3.1 Categories G1-G4

Some PRDs require specific treatments to slow disease progression, for instance kidney diseases of autoimmune aetiology (Glomerulonephritis, Systemic Lupus Erythematosus) are treated with immunosuppressive drugs. Improving glycaemic control in diabetes is likely to slow the progression of CKD[54] as well as reducing cardiovascular risk.[55] Beyond these treatments specific to PRD, CKD treatment aims to reduce the risk of kidney disease progression and cardiovascular disease, by reducing blood pressure, proteinuria and dyslipidaemia with drug treatment, and lifestyle changes such as weight loss, smoking cessation and reduction in salt intake (which also reduces blood pressure).[35]

1.3.2 Renal replacement therapy and conservative care

The term ‘kidney failure’ is used interchangeably with GFR category G5 (previously CKD stage 5, eGFR <15ml/min/1.73m^2) in KDIGO guidance (Figure 1-2). However, ‘kidney failure’ implies the need for RRT, initiation of which is not usually dictated by absolute eGFR, but by the development of the clinical features of kidney failure[56] such as salt and water overload, hyperkalaemia or acidosis. The term ‘ESRD’ indicates that CKD has progressed to the point where RRT would be offered, although variation in clinicians' thresholds for RRT initiation makes absolute definition of ESRD problematic.[57]

RRT includes haemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation. Dialysis treatments mechanically remove waste products, salts and water from the circulation, whereas kidney transplantation uses a donor organ to replace kidney function. 'Conservative care' indicates maximal medical management of CKD without RRT.[58, 59] Dialysis aims to improve uraemic symptoms and prevent the life-threatening consequences of ESRD. Although dialysis replaces many functions of the kidneys, it is less effective at reducing cardiovascular risk: the relative risk of cardiovascular morbidity or mortality in ESRD is higher than during earlier CKD,[2] and age-adjusted five year survival after starting dialysis is around 55%.[60] Further, people receiving dialysis report significantly lower health-related quality of life compared to the general population.[61] Kidney transplantation confers a considerable benefit in comparison to dialysis in terms of cardiovascular risk,[62] mortality,[4] and quality of life[5] for most recipients. For patients who are fit to have transplant surgery and able to adhere to immunosuppressive treatment, transplantation is therefore the preferred method of RRT.

After starting RRT, individuals may change RRT modality or withdraw from dialysis. Such changes are made out of patient preference, because of complications of a dialysis modality (eg: peritoneal dialysis failure, Section 1.3.2.2), after a new transplant, or when a current transplant fails.

1.3.2.1 Haemodialysis

Haemodialysis (HD) is the most commonly used dialysis modality in the UK: 41% of prevalent RRT patients (around 69,000) in the UK received HD in 2014.[49] Patients undergo sessions of treatment on a pump-driven machine to dialyse blood against an electrolyte solution across a semi-permeable membrane. HD sessions are most commonly performed at dialysis units on a hospital site or at a 'satellite' clinical centre. In the majority of cases, the process of setting up and connecting to the dialysis machine is performed by specialist nurses, though some patients perform 'self-care' dialysis in a dialysis unit or 'home HD' in their own home. Self-care dialysis is an example of a shared care initiative aiming to increase patient involvement and activation[63] and outcomes.[64] The typical dialysis prescription is three four-hour sessions per week, though patients on home HD may perform shorter, more frequent sessions, and this increase in dialysis dose is likely to confer a clinical benefit.

To allow adequate blood flow from patient to HD machine, patients must undergo a procedure to establish vascular access. The favoured type of HD access is an arteriovenous fistula: a surgically-formed connection between artery and vein, usually in an upper limb. The fistula is formed by surgery under regional or general anaesthetic. Once the fistula has been formed, a period of several weeks is needed for it to 'mature', after which time needles can be inserted to allow haemodialysis. However, not all fistula surgery is initially successful, and some fistulas will fail,[65] often prompting referral for repeat vascular access surgery. In cases where native vessels cannot be used for fistula formation, synthetic tubes are used to form a arteriovenous 'graft' - these can be 'needled' in the same way as a native fistula and used for dialysis and still have reduced complication rates compared to the alternative - venous dialysis catheters. These are synthetic dual-lumen catheters placed into a central vein (most commonly the internal jugular vein) and externalised over the chest wall. Insertion is performed under local anaesthetic and these can be used for dialysis immediately after insertion. However, use of dialysis catheters is associated with increased risk of infection and mortality compared to fistulae or grafts.[66, 67] Clinical practice guidelines reflect this by promoting early fistula formation to reduce the proportion of patients starting haemodialysis with a venous catheter and the prevalence of catheter use among the haemodialysis population.[68]

1.3.2.2 Peritoneal dialysis (PD)

Peritoneal dialysis is an alternative dialysis treatment which achieves the same goal as HD: solute and water removal, but by a different method. A glucose and electrolyte solution is drained into the peritoneal cavity, which draws waste products, electrolytes and water from blood from the capillaries of the peritoneal membrane into the peritoneal cavity. The fluid is drained out and the process is repeated. 6% of UK RRT patients received PD in 2014.[49] Access to the peritoneal cavity is by 'Tenckhoff' peritoneal dialysis catheter, which is inserted into the peritoneal cavity and externalised over the lower abdominal wall. This requires a day-case surgical procedure. Usually, the catheter is not used for dialysis until several weeks after insertion.

PD is usually performed by the patient in their own home. Two treatment modalities are used. In 'Continuous Ambulatory Peritoneal Dialysis' (CAPD), fluid 'exchanges' are performed around 4 times per day and take around 20 minutes to complete. Alternatively, 'Automated Peritoneal Dialysis' (APD) uses a machine at night which automatically pumps fluid into and out of the peritoneal cavity while the patient sleeps. Both techniques require the patient to connect their Tenckhoff catheter to the fluid bags, perform the exchange or set up the cycler and disconnect once the exchange is complete. An exception is 'Assisted APD' (aAPD), whereby a healthcare professional will 'assist' the patient by connecting and disconnecting the APD machine before and after each session. The major complication of PD is infection, either abdominal soft tissue infection or infective peritonitis, the avoidance of which depends upon maintenance of sterile conditions while performing dialysis. If infections occur, treatment often involves removing the Tenckhoff tube, and may necessitate temporary or permanent transfer to haemodialysis.

In contrast to hospital haemodialysis, the 'home therapies' (peritoneal dialysis and home haemodialysis) require patients to learn how to perform the dialysis treatment safely and deal with any problems. Training is usually provided by specialist nurses from the patient's renal centre. Adequate space to store dialysis equipment in the patient's home is also needed (and for home haemodialysis, a suitable water supply). Home therapies allow increased flexibility with timing of dialysis and maintenance of independence. Compared to haemodialysis, peritoneal dialysis is superior in terms of maintaining some residual kidney function,[69] which provides some solute and water clearance, and may provide a clinical advantage.[70]

1.3.2.3 Dialysis adequacy, Anaemia and Bone metabolism

The dose of dialysis delivered to an individual is recorded by measuring the reduction in urea. Urea clearance is expressed either as the fractional reduction in urea during a dialysis session (Urea Reduction Ratio, URR) or as Kt/V, a measure taking into account urea clearance (K), dialysis session time (t) and the volume of distribution of urea (V). Other markers of dialysis adequacy include pre-dialysis potassium and bicarbonate levels, and serum albumin, which reduces as a marker of poorer nutrition or increased inflammation.

Anaemia in ESRD caused by Erythropoietin deficiency (Section 1.1.3) is treated with synthetic Erythropoietin analogues, given subcutaneously or intravenously on the dialysis machine. Supplemental iron is also given. Haemoglobin and ferritin are routinely measured to guide these treatments.

Disorders of bone metabolism (Chronic Kidney Disease-Mineral Bone Disorders; CKD-MBD) are managed using supplements of activated vitamin D, dietary restriction of phosphate, and phosphate binding medications. CKD-MBD is monitored by measuring serum phosphate, calcium and intact parathyroid hormone levels.

Together, these measurable variables are used to assess the overall quality of dialysis treatment and in the UK, target values are dictated by the Renal Association, and termed 'dialysis quality indicators' (QIs).[71] The UK Renal Registry[72] collects and reports data on dialysis quality at UK renal centres, including measurement of these dialysis quality metrics.

1.3.2.4 Kidney transplantation

Kidney transplantation is the most prevalent form of RRT in the UK: 53% of RRT patients have a kidney transplant.[49] Donor kidneys for transplantation are obtained from a deceased donor who has agreed to donate their organs after death or from a living donor. The majority (64% in 2014) of donor kidneys in the UK are from deceased donors.[73] Several terms are used to classify transplants by donor, recipient and procedure type, summarised in Table 1-3**.**

Table 1-3: Kidney Transplantation glossary of terms

DBD: Donor after brainstem death **DCD: Donor after cardiac death** **ECD: Extended criteria donor**	DBD donors are brainstem dead but have a cardiac output at the time of organ retrieval. DCD donors have no cardiac output at the time of retrieval (organs are retrieved as soon after loss of cardiac output as possible). This classification is made because DCD kidneys are more prone to ischaemic injury (during the period of time from loss of cardiac output to kidney reperfusion). Although DCD kidneys have higher rates of delayed function, longer term outcomes are comparable.[74] ECD donors are DBD donors with characteristics which predict poorer transplant outcome such as hypertension or age over 60 years. In the UK, potential transplant recipients can specify in advance whether they would wish to accept a kidney from an ECD donor.
LKD: Living kidney donor **Non-directed ('altruistic') donor** **Paired organ exchange** **HLAi: HLA incompatible** **ABOi: ABO incompatible**	The majority of living kidney donors are known to the recipient, but some donors are 'non-directed altruistic' donors, who donate organs to a recipient not known to them. If a potential living donor does not have a compatible HLA or ABO type to the relative or friend to whom they wish to donate, a paired kidney exchange is sometimes organised. Another option in this situation is ABO or HLA incompatible transplantation, whereby enhanced immunosuppression, usually with plasma exchange, is given to the recipient before and after transplantation to allow transplantation of an organ which is not compatible by ABO or HLA type.
SPK: Simultaneous Pancreas and Kidney transplantation **Kidney and heart, liver or bowel transplant**	Patients with Type 1 diabetes (who by definition have absent endocrine pancreatic function) who develop ESRD may have simultaneous kidney pancreas transplantation to treat both diabetes and ESRD. Dual organ transplants (kidney and heart, kidney and liver etc.) are sometimes performed in patients with dual organ failure.
Pre-emptive transplantation	Pre-emptive transplantation is performed before the recipient reaches ESRD.

The majority of kidney transplant recipients receive a transplant after starting dialysis. However, 'pre-emptive' transplantation before dialysis allows direct transition from impending ESRD to transplantation. Minimisation of time of dialysis is preferable because it avoids associated increases in cardiovascular risk.[75] However, the absolute advantages of pre-emptive transplantation are hard to define because of differences in demographics between the general transplant population and those receiving a transplant pre-emptively, who are more likely to be white, have higher SES and less likely to have diabetes.[76]

1.3.2.5 Kidney transplant matching and allocation

In the majority of cases, transplant kidneys are required to be 'matched' to the ABO blood type and Human Leukocyte Antigen (HLA) type of the recipient. The matching process aims to reduce the likelihood of transplant 'rejection': transplant damage caused by the recognition of donor tissue as 'foreign' by the recipient's immune system, which can cause transplant failure. Because the supply of deceased-donor organs is exceeded by demand, 'waiting list' systems operate, aiming to use donated organs in a way which is equitable, and to maximise the net benefit to the population. In the current UK system, the level of immunological matching, recipients' accrued time on the transplant list, recipient age, donor-recipient age difference and the geographical location of the donor kidney relative to the donor are taken into account when allocating kidneys to recipients.[77] Kidneys from donors after brain death (DBD) are allocated via a national pool, whereas kidneys from donors after cardiac death (DCD) are allocated regionally, with one kidney from each donor allocated to the transplant centre nearest to the location of the donor.[77] This aims to reduce the amount of time from kidney retrieval to restoration of blood supply in the recipient ('cold ischaemic time') for DCD kidneys, which are prone to more ischaemic injury than DBD kidneys because of the cessation of blood flow before retrieval (Table 1-3).

Before being added to the deceased-donor transplant waiting list or considered for a living-donor transplant, potential transplant recipients must be deemed fit to have a transplant operation (to reduce the risk of perioperative death or illness) and must be free of comorbidities which are contraindications to transplantation (for instance, cancers or active infection). This may require additional outpatient appointments or investigations, for instance to establish cardiac fitness in groups with risk factors for cardiovascular disease.

1.3.2.6 Living donor selection process

Relatives or friends of patients with CKD or ESRD may offer themselves as potential kidney donors. Less commonly, 'non-directed', 'altruistic' donors without any direct relationship to someone with ESRD may donate a kidney for use by anyone in need of a transplant. Potential donors are investigated to establish their fitness to undergo surgery and to exclude those for whom donating a kidney may pose a risk to their long-term health. These appointments, and the donor-nephrectomy surgery itself, require donors to take time away from employment and other daily activities. Reimbursement schemes are in place to prevent financial loss to the donor, aiming aim to provide neither a financial incentive nor disincentive to donation.[78]

1.3.2.7 Transplant Surgery and follow-up

Kidney transplant recipients undergo surgery to implant a donor kidney, either at the time when a deceased-donor kidney becomes available, or as an elective procedure in the case of living donation, followed by a hospital stay of several days. There follows a period of frequent outpatient follow-up which reduces in intensity over the weeks to months after transplantation. Initially, this involves appointments 2-3 times per week, often at a regional transplant centre, which may be further from the patient's home than their usual renal centre. During these appointments, patients are monitored for complications of transplantation and doses of medications are altered regularly. Patients may be readmitted to hospital to deal with any complications. In the long-term (after 3-6 months), transplant function is likely to be stable but patients may still experience acute problems requiring medical input. Transplanted kidneys can decline in function and fail (5 year graft survival in the UK is 87%[79]) so it is common for patients to return to dialysis or receive a further transplant. As transplant function declines, patients are again at risk of the complications of CKD.

1.3.2.8 Complications of kidney transplantation

Complications of kidney transplantation relate to the anatomy of the transplant itself, or to the immunosuppressive treatment required to prevent rejection. They vary in incidence depending on the time after transplantation (Table 1-4), and may require increased frequency of clinics, investigations (including transplant kidney biopsies) or in-patient treatments.

Table 1-4: Complications of kidney transplantation

	Complication	Treatment
Surgical and anatomical complications	Ureteric stenosis(narrowing) causing urinary obstruction Urine leak from breakdown of the ureteric anastomosis (connection of transplant ureter to recipient's bladder)	May require surgical repair, stenting, external drainage of urine (nephrostomy)
	Transplant artery and vein- stenosis or breakdown of anastomosis	May require surgical repair or angioplasty/stenting
Infections	Bacterial infections as a result of surgery Atypical infections or viral infections as a result of immunosuppression	Require antibiotic treatment, changes in immunosuppression, further investigations. Often hospital admission
Transplant Rejection	Rejection can occur at any stage, but most common early in the transplant course	Requires transplant kidney biopsy for diagnosis, and additional immunosuppressive treatments. Some of these are given as prolonged courses of intravenous treatment, often necessitating hospital admission
Malignancy	Increased risk of malignancies driven by viral infections, for instance Epstein-Barr Virus-driven Post Transplant Lymphoproliferative Disorders (PTLD), HHV8-driven Kaposi's sarcoma etc.	Will require changes in immunosuppression; may require chemotherapy
	Increased risk of non-melanoma skin malignancy	Often require surgical intervention and active follow-up from a dermatologist

1.3.2.9 Conservative care of ESRD.

As comorbidity and age increase, the potential benefit of RRT in extending life reduces,[80] while potential burdens of RRT are likely to increase. Comorbidity and dependence may preclude transplantation or 'home' dialysis therapies, meaning that RRT is likely to take the form of hospital haemodialysis. Preparation for haemodialysis includes vascular access procedures, which may be less likely to be successful in older individuals.[81] Thrice-weekly haemodialysis itself, with its associated transport arrangements may present a significant burden on the patient and their carer.

Conservative care involves management of ESRD with medical treatment, but without dialysis. Decisions to opt for conservative care are often made in advance of development of ESRD when any benefit of dialysis is felt to be outweighed by the burden of preparation for and receipt of dialysis treatment.[58] The arrangements for delivery of conservative care in the UK is variable between renal centres.[58] Patients included in the ATTOM study (data from which is used in the novel research in this thesis) were aged 18-75 years, and many of the studies included in systematic reviews in Chapter 1: excluded older, more comorbid patients. As such, the investigation and discussion in this thesis focusses upon those opting for some form of RRT and not for conservative care.

1.3.2.10 UK Trends in RRT provision

Between 1980 and 2004, the number of UK patients starting RRT per year rose from around 20 pmp to 115 pmp, and this incidence has remained at a similar level in subsequent years.[48] Much of this increase is accounted for by a significant rise in the number of people aged over 65 years starting dialysis, which rose from 100 to 300 pmp between 1992 and 2002. There has been a corresponding increase in RRT prevalence, which was 913 pmp in 2014 compared to 157 in 1982,[82] explained by steady increases in the number of patients living with a kidney transplant, as well as increases in people receiving maintenance hospital HD.[49] Although prioritisation of home therapies is now recommended,[68, 83] the prevalence of maintenance PD has reduced,[49] and the incidence of PD has remained unchanged since 2009.[48] In response to the increased need for renal services, the number of renal centres has increased. [84] Currently there are 71 renal units in the UK. Only 24 of these are transplanting centres: a structure that aims to ensure quality by increasing the number of transplants performed at transplanting units.

Patient survival at one year after starting dialysis has increased over the last ten years.[60] In 2013, 89.9% of patients on haemodialysis and 93.4% of those starting peritoneal dialysis survived for more than one year. Those starting peritoneal dialysis are younger and have lower levels of comorbidity,[60] so this survival difference should not be attributed to dialysis modality. In the same way, it is problematic to directly compare survival rates between patients receiving dialysis and patients after transplantation because of differences in comorbidity. Five-year survival after transplantation in 2008-2010 in the UK was 87%.[79]

From a total of 3,263 single-organ kidney transplants performed in the UK in the 2015-2016 financial year, 41% were from DBD donors, 28% DCD and 32% from living donors.[79] There has been an overall trend in recent years to increase the use of DCD organs,[85] and since 2009/10 the number of patients on the deceased-donor waiting list has progressively fallen from a maximum of 7,190 in 2008/9 to 5,275 in 2015/16. In 2015-16, 22% of kidney-only transplant recipients received a 'pre-emptive' transplant (before starting dialysis).[79] In general, the HLA types represented in the UK donor pool reflect the population of the UK, although rates of donation are lower among non-white UK residents. Potential transplant recipients of non-white ethnicity are therefore less likely to be offered well-matched kidneys once on the waiting list. This is recognised as a potential barrier to transplantation for ethnic minority recipients.[85] The median waiting time for a deceased-donor transplant in the period 2009-2013 was 944 days (95% CI: 924-964), around 2 years 7 months.[79] This means that although transplantation is the preferred RRT modality for the majority, a large number of patients will remain on dialysis for a significant period while waiting for a transplant offer, and be subject to increased morbidity and mortality during this period.

1.4 Patient pathways in CKD

This section outlines patients' pathways of disease and treatment in CKD (Figure 1-4), with the aim of giving an insight into the design of renal services and the interaction between patients and clinicians at various points in these pathways. This will allow an understanding of the potential role of patient factors including socioeconomic status and health literacy (Chapter 2) in influencing patient outcomes.

CKD diagnosis is usually made when kidney function is checked by blood testing, which can occur in a variety of settings. In the UK, screening for CKD by GFR estimation is recommended in people with known diabetes, hypertension, AKI, cardiovascular disease, structural renal tract disease, multisystem diseases which can cause CKD (eg: SLE), family history of CKD or incidental non-visible haematuria.[27] Diagnosis of CKD is confirmed by repeat eGFR measurement as described in section 1.2.4. If an individual is not known to have any of the above conditions, CKD may remain undiagnosed.[46, 86] Further, because many (especially elderly) patients who are classified as having early CKD are at little increased risk of morbidity and mortality, there may be a reluctance among clinicians to 'label' them with a diagnosis of CKD.[87] Because symptoms of kidney disease are often absent until stages G4-G5, a number of patients are likely to die with undiagnosed CKD, and it is not uncommon in clinical practice for patients to present to renal services at the point of reaching ESRD. The proportion of incident dialysis patients presenting to renal services within 90 days of dialysis start ('late presentation') is recorded as a marker of service quality by the UK Renal Registry.[48]

After CKD diagnosis, CKD management is initiated (Section 1.3.1). ‘Quality Outcomes Framework’ (QOF) lists,[88] (introduced for CKD in 2006 and developed since) allow GP practices to register appropriate monitoring and treatment of CKD patients, linked to financial incentives. Referral to secondary care nephrology services is made according to clinical need. NICE recommends referral for those with GFR categories G4 and G5, in those with a sustained decrease in eGFR of 25% or more, in those with significant albuminuria (ACR category A3), in cases of difficult-to-control hypertension, or in those with suspected rare causes of CKD or suspected renal artery stenosis.[27] In secondary care, management of PRD, cardiovascular risk and risk of progression continues and patient education and planning for RRT or conservative care is initiated. Timing of preparation for RRT or conservative care depends on the rate of CKD progression and estimated time to ESRD. The UK Renal Association recommends referral to secondary care at least 1 year before the anticipated date of ESRD to allow time for adequate preparation for RRT if appropriate. Activity to promote early (6 months before expected date of ESRD), pre-emptive transplant wait-listing and living-donor pre-emptive transplantation is recommended. Recommendations for dialysis preparation include early referral for dialysis access and promotion of home dialysis. Figure 2-1 also shows that once ESRD is established, patients may transfer from dialysis to transplantation, back to dialysis, or withdraw from dialysis. They may also change between dialysis modalities.

Embedded within UK guidelines on CKD management are the ideas of shared decision-making and self-care (Section 1.5). Guidelines on choice of dialysis modality directly recommend shared-decision making.[71] Home dialysis is promoted because it promotes self-care. Where home dialysis is not possible, other self-care activities are encouraged, such as active involvement in dialysis treatment.[64, 71] Other services designed to encourage patient participation include Renal Patient View: an online portal which allows patients to access blood results and clinic letters at home, with the aim of empowering patients to monitor their kidney disease and treatment.[89]

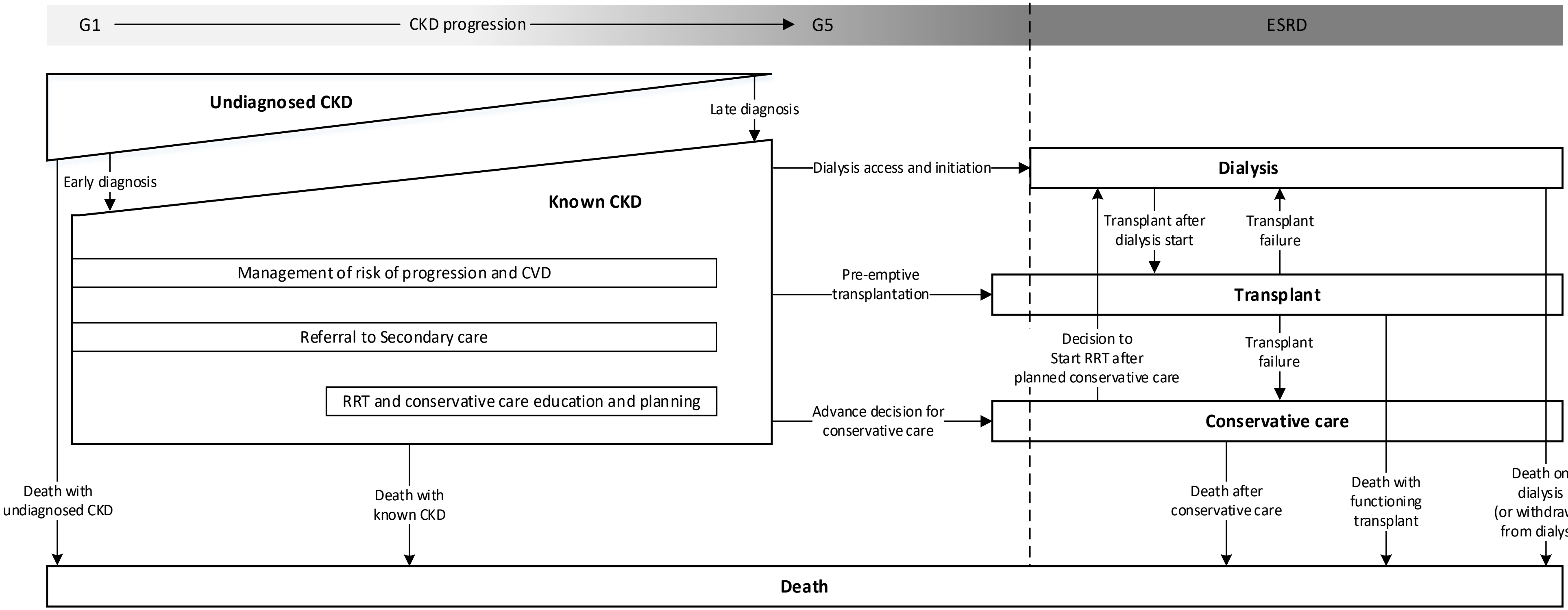


Figure 1-4: **CKD patient pathway**

1.5 Self-care and shared decision-making

The promotion of self-care and shared decision-making activities in the care of CKD is part of a widespread trend in healthcare policy. The Chronic Disease Self-Management program, developed in the late 1990s in the USA, recorded improvements in health status and reductions in healthcare expenditure among people with chronic diseases,[90, 91] and led to widespread promotion of similar initiatives. The UK 'Expert Patients Programme', established in 2002 by the Department of Health, but now run as a Community Interest Company, delivers training for patients with chronic diseases to promote self-management and independence.[92] Most recently, the goal of increasing patient involvement in decisions about their health is set out in the 2015 NHS England constitution.[93] The King's Fund publications 'Making Shared Decision Making a Reality' (2011)[94] and 'People in control of their own health and care' (2014)[95] also promote these goals. These policies have led to the development of NHS resources to facilitate shared decision making, including online decision aids.[96]

The concept of patient-centred care is driven by several principles. Firstly, healthcare professionals have an ethical duty to inform patients about their care. Second, patients as consumers and as citizens have a right to be involved in the process of receiving care. Third, providing care to patients based on their preferences has potential to increase the effectiveness of care: patients are more likely to receive the care they want. Last, empowering patients to take control of their treatment may encourage a culture of increased responsibility for one's own health, with scope to improve adherence to treatment and to lifestyle measures such as exercise and healthy eating.[95]

Shared decision-making is a key aspect of patient-centred care, and is defined as:

> *'an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences.'*

Shared decisions should be informed both by clinical evidence, known mostly by the clinician, and by patients' preferences, known only to the patient. [94, 97] The importance of patient involvement in decisions is highlighted by evidence that clinicians cannot accurately predict patients' preferred choices.[98] Family or carer preferences are also important to the patient when making decisions about care.[99] Patients not only report wanting to be more involved in decision making,[99] but treatments based on shared decisions lead to improved patient satisfaction.[100] However, patient involvement in clinical decisions still appears to be lacking, evidenced by the significant variation in treatment practice in multiple areas of healthcare.[101] Variation in practice is driven by variation in healthcare resources (for instance, higher use of specific surgical procedures in centres employing a surgeon with expertise in that procedure), and by clinician preference.[98] Within kidney care in the UK, there is significant regional variation in rates of peritoneal dialysis treatment compared to haemodialysis, and recognised differences between renal centres on uptake of renal replacement therapy[102] or transplant wait-listing,[103, 104] whereby patients treated nearer to centres where dialysis or transplantation are performed are more likely to receive these treatments. This variation suggests a significant effect of clinician or centre preference on treatment decisions. Efforts to promote shared decision-making in kidney care are therefore being made,[105] with the intention of promoting individualised treatment choice (and as a consequence, reducing regional or centre variation in practice).

Promotion of patient involvement in care and decision making therefore has many potential benefits. However, increasing the role of CKD patients in care and decision-making requires them to understand complex concepts, for instance, understanding and balancing the benefits of dialysis vs conservative care, peritoneal dialysis versus haemodialysis, or the advantages of proceeding with work-up for kidney transplantation despite the extra appointments and investigations it initially requires. Although people with CKD report wishing to receive more information about their disease and treatment, this does not necessarily imply a wish to be involved in decisions.[106] There may be a risk that allocating responsibility for care and decision making to the patient could add to the burden of work required of the patient in managing disease.[107] This is relevant to the cumulative complexity model of chronic disease, discussed in section 2.3.

1.6 Conclusions

This introductory chapter outlines the pathology and treatment of CKD, and how this translates to pathways of disease and treatment for the patient. This background should allow the reader to understand the potential effects of patient characteristics such as SES and health literacy on processes and ultimately outcomes of care in CKD. The complexity of the information contained within this chapter, especially relating to RRT, demonstrates the difficult concepts which patients are required to understand in order to succeed with self-care and shared decision-making activities.

Chapter 1: Introduction to chronic kidney disease

Chapter 2 introduces the concepts of SES and health literacy. The potential effects of these factors on patients' success in navigating the CKD patient pathway are discussed with reference to the cumulative complexity model: a theoretical model of patient complexity, which describes the factors influencing patients' ability to manage their disease and treatment.

Chapter 2: Socioeconomic status, health literacy and the cumulative complexity model of disease

The patient pathway shown in Figure 1-4 illustrates the processes by which CKD care is delivered. Healthcare systems (especially in countries providing universal healthcare such as the UK) aim to provide healthcare according to individual need. As such, the provision of healthcare services is unequal, aiming to provide services to those who need them most. However, factors other than clinical need have also been shown to influence access to services and health outcomes, including ethnicity or socioeconomic status. Inequality related to these factors, which results in injustice or unfairness in care, is referred to as 'inequity'.

This chapter describes evidence of socioeconomic inequity in health and healthcare, in general and within CKD. The concept of health literacy is introduced along with the known associations of health literacy outside CKD populations. This allows an understanding of the mechanisms by which health literacy may influence care in CKD, and potentially mediate the effects of SES on health outcomes. These mechanisms are investigated in Chapters 3 to 6.

2.1 Socioeconomic status and health inequity

2.1.1 Socioeconomic status in general populations

Low SES is an established risk factor for adverse health outcomes worldwide.[108] The concept of SES encompasses more than just financial capital, and has been defined as:

> *'the relative position of a family or individual on a hierarchical social structure, based on their access to or control over wealth, prestige and power.'*[109]

Even in the UK, where healthcare is free at the point of use (and access to healthcare services is not directly influenced by low income), there are significant differences between in health outcomes between socioeconomic groups. SES-related health disparities were highlighted in the 2010 Marmot report.[110] Figure 2-1 illustrates the marked variation in life expectancy and disability-free life expectancy between areas of England with differing levels of area deprivation (a proxy for individual SES, see below).

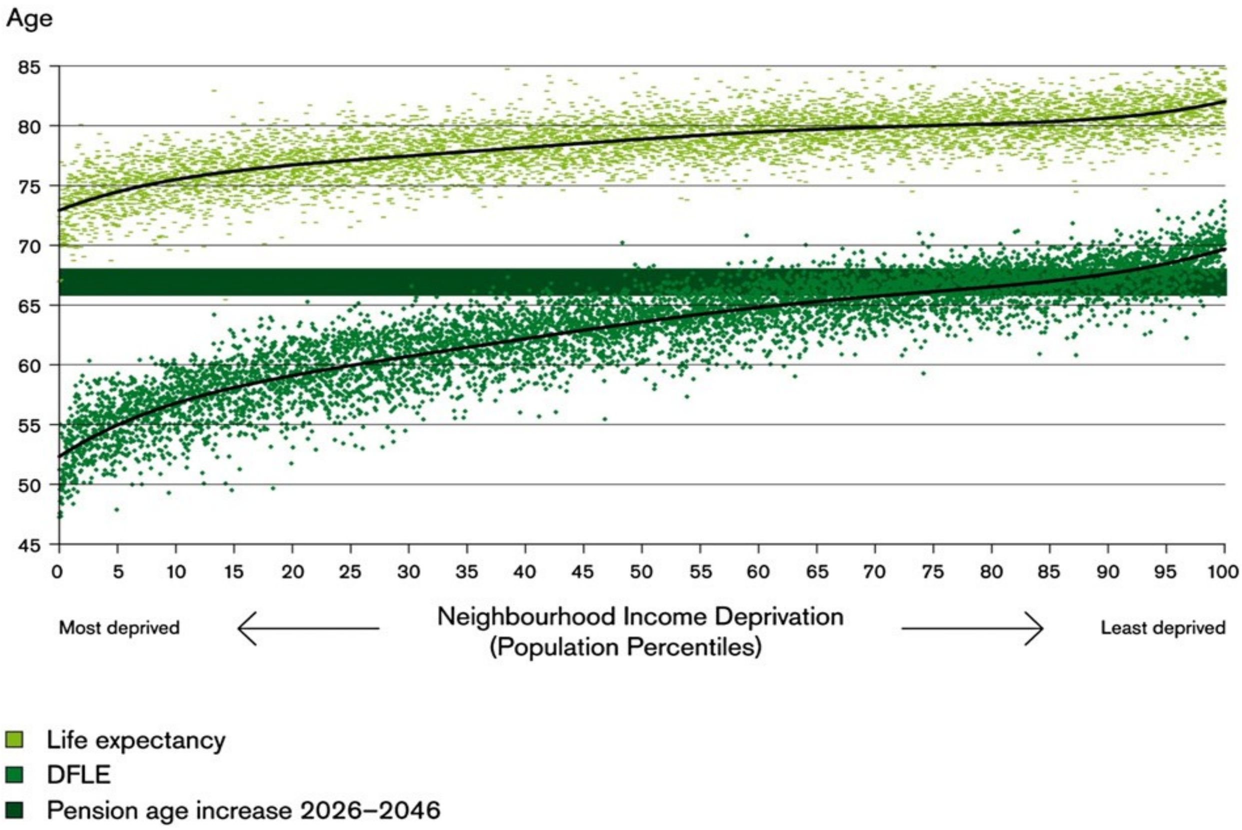


Figure 2-1: Life expectancy and disability-free life expectancy at birth by neighbourhood income deprivation, England, 1993-2003

Marmot review 2010.[110]

Low SES is hypothesised to lead to poorer health outcomes by multiple determinants of poor health which are more prevalent among those with low SES, and do not relate to healthcare provision.[111-113] Features of low SES as categorised by low education, income and occupational class may have direct effects on health, or affect health via mediating factors. Some of these hypothesised relationships are shown in Figure 2-2. Potential mediating factors include exposure to environmental risks (poor air quality, noise, passive smoking), unhealthy behaviours which are driven by social determinants (smoking, alcohol, diet), poor housing, poor work conditions, and reduced access to healthcare in those with low socioeconomic status (and associated high morbidity[114]: the 'Inverse Care Law'[115]). This thesis investigates whether health literacy may act as a mediator in this pathway within CKD care (Chapter 6).

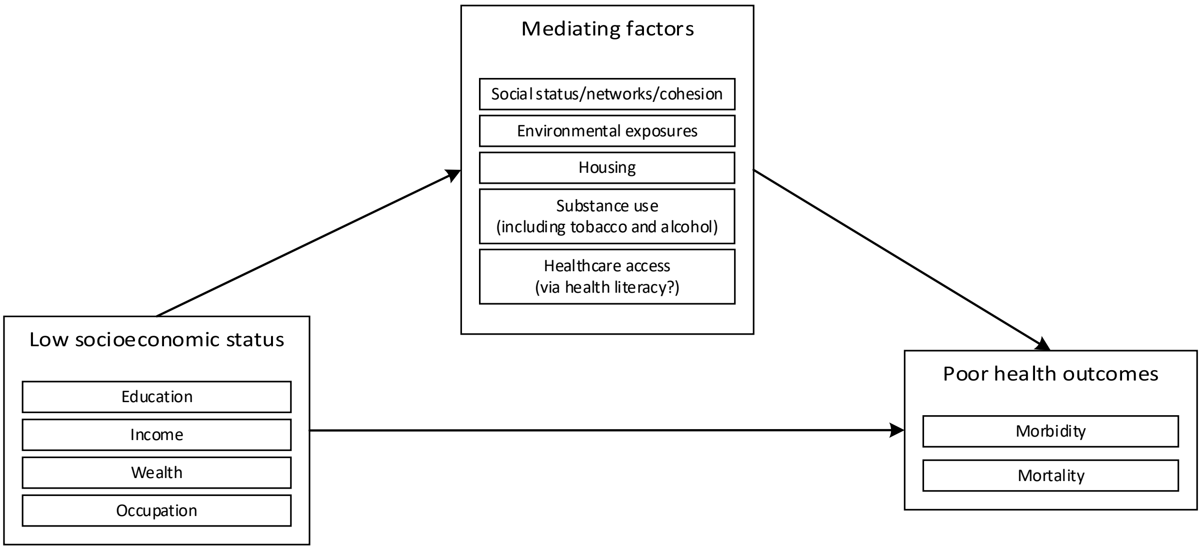


Figure 2-2: Hypothesised relationships between low socioeconomic status and health outcomes.[112, 113]

The multiple facets of SES, and the complexity of associations between SES and health outcomes makes measurement of SES in health research difficult: no single measureable factor encompasses the whole concept. Therefore, multiple strategies are used to attempt to measure SES for an individual. At the level of the individual, markers of SES include wealth, access to transport, housing tenure, occupational class, education and employment.[116] In population studies of SES, direct data collection of individual SES data may not be feasible, so area-level measures of SES are often used. These include the Index of Multiple Deprivation(IMD),[117] a composite score of historical data on average level of income, employment, disability, education, housing, crime and living environment for a small geographical area. In epidemiological studies, the use of area-level SES measures has some advantages: data are easier to collect for large populations and take into account several markers of low SES. Disadvantages include the application of an area-level measure to an individual, leading to misclassification.[118]

2.1.2 Socioeconomic status in CKD

Many differences in patterns of disease and treatment by SES have been reported in CKD. Socioeconomic status is thought to influence the risk of CKD from early life.[119] The prevalence of CKD and albuminuria is increased in populations with reduced SES. [120-123] The high prevalence of CKD in deprived populations in the UK results in a higher number of CKD patients per GP in deprived areas,[123] which is likely to lead to reduced access to primary care CKD management among those with low SES. Further, the system of rewarding primary care practices who attain quality targets dictated by the Quality Outcomes Framework risks underfunding of practices which serve deprived populations (and does not take into account the increase in work required to attain these targets in these areas).[124] These factors, combined with the higher prevalence of comorbidity and risk factors for progression[114] may explain differences in the severity of CKD at presentation to secondary care renal services: those with low SES present with more advanced CKD (Figure 2-3).[125]

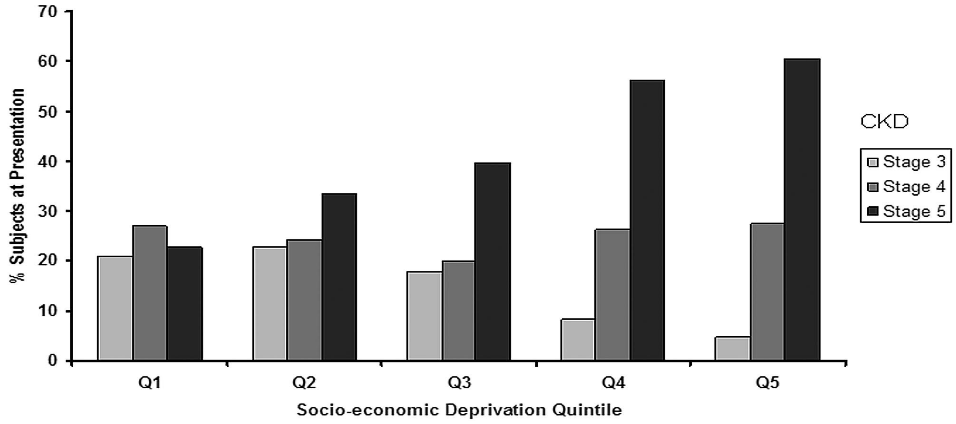


Figure 2-3: Distribution of patients in CKD stages 3-5 at presentation to secondary care renal services

By Index of Multiple Deprivation quintile (Q5 being the most deprived). From Bello et al. (2008).[125]

Low SES is associated with increased incidence of ESRD,[102, 126] but reduced access to peritoneal dialysis (which has some advantages over haemodialysis; section 1.3.2.2).[127, 128] Survival on RRT is reduced in those with low SES,[8] accounted for in part by increased comorbidity, smoking and reduced adherence to treatment. Low SES in the UK is associated with reduced access to the deceased-donor transplant waiting list. In England and Wales, the hazard ratio for deceased-donor transplant wait-listing is 0.6 (95% CI: 0.5-0.7) for the most deprived IMD quintile of white patients compared to the least deprived.[9] Similar results have been reported in Scotland.[104] Rates of living-donor transplantation are also reduced: the hazard ratio for living-donor transplantation is 0.4 (95% CI: 0.3-0.5) for the most deprived quintile compared to the least deprived.[10] This reduction in the rate of living-donor transplantation may be explained in part by reduced living kidney donation.[129] Similar associations have been shown in USA studies.[130, 131] After transplantation, UK patients with lower SES have been shown to have increased mortality, independent of comorbidity differences.[132]

This thesis also considers the effect of SES on CKD outcomes in the USA. The structure of USA healthcare systems should be taken into account when interpreting this data. For instance, the US insurance-based healthcare system is likely to reduce access to healthcare services for those with low SES. Kidney transplant recipients in the US receive insurance cover for their immunosuppressant drugs for a set time only, after which they are required to self-fund.[133] This arrangement is likely to result in reduced transplant outcomes for those with low SES. Strong associations between black and Hispanic ethnicity and low SES in the USA[17] result in marked disparities in clinical outcomes between ethnic groups, including in CKD.[134]

In summary, there is established evidence of SES-related disparities in access to treatment and outcome throughout the CKD care pathway. Many of the mechanisms by which low SES may influence health outcomes (Figure 2-2) are societal factors outside the direct control of healthcare service providers. However, disparities in access to healthcare may be promoted by the way in which healthcare services are delivered. The next section introduces the concept of health literacy, and the idea that low health literacy may reduce patients' ability to successfully access healthcare services. By its association with low SES, low health literacy may mediate the effect of low SES on outcomes.

2.2 Health Literacy

In a 1993 study, 90 million adults (of 191 million) in the USA had literacy graded in the lowest two levels of a five-point scale.[135] Individuals with this level of literacy were able to complete simple, one-stage tasks such as calculating the total cost of two items or finding a junction on a street map, but were unlikely to be able to complete more complex tasks involving more than one sequential step. Lower literacy was associated with poverty, reduced employment, lower levels of voting and higher levels of imprisonment, and hence was hypothesised to impair individuals' level of function in ordinary life. This prompted investigation into literacy as a determinant of health,[136, 137] and identified a mismatch between information provided to users of healthcare services and their level of understanding.[138] Poor literacy skills were identified as a potential barrier to effective clinical care (or good literacy skills as an asset allowing an individual to more successfully control their health and healthcare[139]). The potential for literacy to improve with education or experience,[140] or for changes in healthcare policy to improve outcomes among those with low literacy[13] has led to the rapid expansion of research.

2.2.1.1 Definitions

The term 'health literacy' has come to define an attribute specific to health and distinct from general literacy (including skills other than reading and writing). Multiple definitions of health literacy exist, and the focus of these definitions has changed over time: earlier definitions described health literacy as a concept dictated only by individual,[141] whereas later definitions changed to take into account the role of social resources and healthcare systems in influencing understanding (‘public health literacy’). A 2012 systematic review of health literacy models and definitions attempted to integrate definitions of health literacy, resulting in the following definition, which combines **individual and public health literacy:**

> *‘people’s knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning* ***healthcare, disease prevention and health promotion*** *to maintain or improve quality of life during the life course’*

This global definition is summarised in a schematic diagram shown in Figure 2-4. An altered definition was also developed, restricting the concept to **individual health literacy:**

‘people’s knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning ***being ill, being at risk and staying healthy,*** *to maintain or improve quality of life during the life course.’*[12]

This thesis investigates *individual* health literacy in people with CKD. Therefore, the term ‘health literacy’ is used to indicate ‘individual health literacy’ unless otherwise specified.

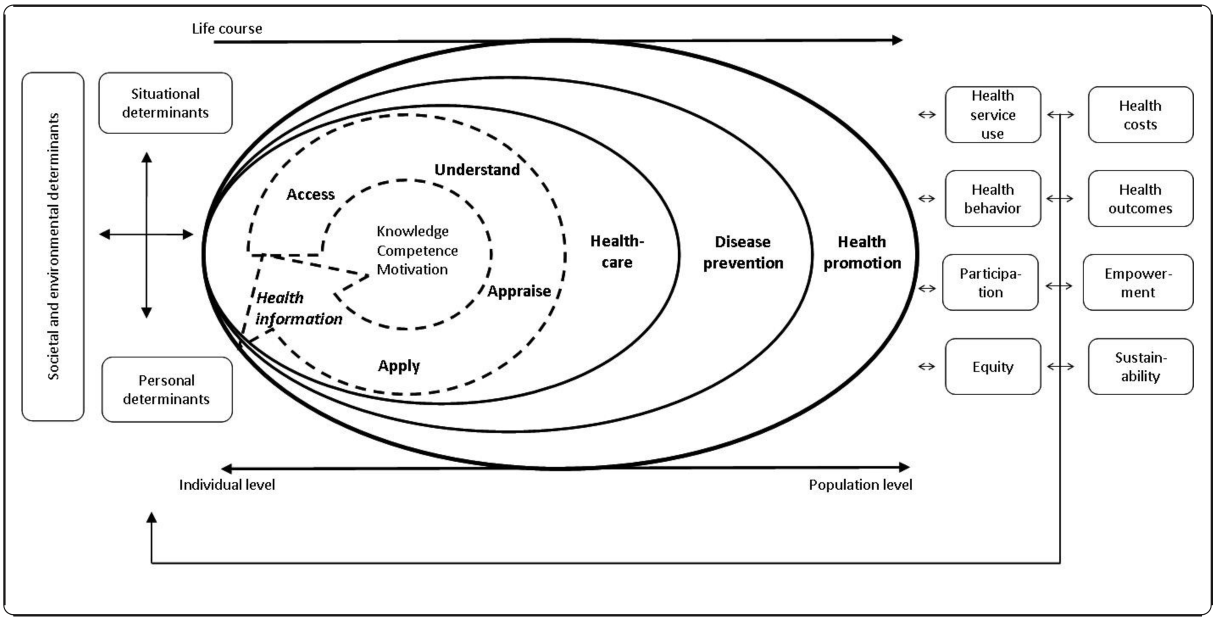


Figure 2-4: **Integrated model of health literacy.**

From Sorensen et al 2012[12]

These definitions, as with the World Health Organisation definition, define four competencies of individual health literacy: the ability to access, understand, appraise and use information[142]. These competencies are used by the individual to process information in three settings: healthcare (‘being ill’), disease prevention (‘being at risk’) and health promotion (‘staying healthy’). The model of health literacy in Figure 2-4 also illustrates some of the consequences of health literacy differences to society. Importantly, these include differences in health costs, outcomes and equity.

Although health literacy has a broad definition, it should be distinguished conceptually from other related concepts:

- It is important to separate health literacy from understanding difficulties related to language fluency, an issue that may present practical difficulties when trying to measure health literacy in English-speaking countries among ethnic minorities whose first language isn’t English. Health literacy measures in different languages have been used, but present difficulty in comparing results between patients with different first languages.
- Although the development of cognitive impairment may impair health literacy skills, the definition of health literacy accounts for other factors which may influence understanding and function. It is possible for an individual with significant cognitive impairment to have adequate health literacy, and for those with adequate cognition to have low health literacy.
- ‘Patient activation’, defined as ‘motivation, knowledge, skills and confidence to make effective decisions to manage health’, is also subject to extensive research. Although people with adequate health literacy are more likely to have higher levels of activation, the two concepts are distinct from one another and show independent associations with health outcomes.[143]
- Numeracy is a distinct skill, which can be applied in healthcare settings to allow (for instance) management of medications or keeping appointments, and as such, numeracy skills fall within the wide definition of health literacy shown above. Some health literacy measures include specific numeracy assessments,[144] but the associations and effects of numeracy in healthcare settings have also been studied separately.[144, 145]
- Health literacy may be disease-specific: an individual may become health literate in diabetes as a result of intensive education, but remain poorly health-literate for CKD.

- Health literacy is acknowledged as a contributor to patient capacity (Section 2.3),[146] but capacity includes other concepts such as physical functioning and social capital, linked to SES.

2.2.1.2 Measuring health literacy in the individual

To investigate the effects of differences in individual health literacy on health outcomes, it is necessary to measure health literacy. In common with the many changing definitions of health literacy, multiple differing health literacy measures have been developed.[147, 148] A description of commonly-used health literacy measures is shown in Table 2-1, and extracts from some measures are shown in Appendix A. The term 'limited health literacy' describes an inadequate level of health literacy, below the minimum needed to successfully manage one's health, and equivalent to below USA 'sixth grade' reading level (in the USA, most 'sixth grade' pupils are aged 12). Limited health literacy is defined within many measures (Table 2-1), and using these definitions in research allows (to an extent) comparison of associations with limited health literacy between studies using different measures (Chapter 3).

Individual health literacy measures assess health literacy by different methods, reflecting the variation in definitions of health literacy and the variety of clinical or research settings in which health literacy is measured. One major distinction between health literacy measures is that some are direct assessments of comprehension, whereas others (often screening tools) ask individuals to rate their level of understanding or need for help in various situations, focussing on the effects of low literacy on patients' function. Some 'disease-specific' health literacy measures[149] may provide more accurate information about an individual's ability to manage one condition, but less about their ability to manage other conditions or their 'general' health literacy. Disease-specific measures make it difficult to compare the health literacy of different healthcare populations.

The advantage of comprehension assessments of health literacy is that they directly measure several competencies in health literacy for an individual. The most commonly used comprehension measures are the Rapid Estimate of Adult Literacy in Medicine (REALM) and the (Short) Test of Functional Health Literacy in Adults ((S)TOFHLA). Such measures may be less useful in larger studies because of their long administration times. Screening tools, which often take the form of between one and three short questions mostly take less than a minute to complete, so are more practical for larger studies. However, there are concerns about the sensitivity and specificity of screening tools compared to comprehension assessments. Validation studies have therefore been performed, where screening tools are compared to comprehension assessments in their ability to detect limited health literacy as defined by comprehension assessments (usually REALM or STOFHLA).[150-152]

Variation in health literacy measures makes comparison of the results from studies using differing measures difficult (Chapters 3 and 4), but comparison is made easier by validation studies. Most commonly, health literacy screening tools have been validated by testing their ability to detect limited health literacy as defined by REALM or STOFHLA.

Table 2-1: Health Literacy measures

	Health Literacy measure	Form	Approximate time taken	Health Literacy categorisation
Comprehension tests	**Short Test of Functional Health Literacy in Adults** [153] (STOFHLA, Appendix A.1))	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 Literacy in Medicine [154] (REALM, Appendix A.2)	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-SF (Short Form of REALM)	7 health-related words tested for pronunciation accuracy	2-3 minutes	0-3 Inadequate 4-6 Marginal 7 Adequate
	Newest Vital Sign [144] (NVS, Appendix A.3)	Six-item assessment of reading comprehension from an ice-cream nutrition label	6 minutes maximum (average 2.9 minutes)	0-1: High likelihood marginal/inadequate 2-3: Possible marginal/inadequate 4-6: Adequate (<4 deemed limited health literacy)
Ratings of understanding	**Brief Health Literacy Screen**[152] (BHLS)	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)	<1 minute	3-8 (or 0-5): Lower 9-14 (or 6-12): Moderate/Higher (<10/15 or <6/12 indicates limited health literacy)
	Health Literacy Survey-European Union[155] (HLS-EU-Q47)	47 questions on a five-point Likert scale. Total score transformed into a 0-50 score.	20-30 minutes	0-25: Inadequate 26-33: Problematic 34-42: Sufficient 43-50: Excellent (Limited= Inadequate + problematic)

	Health Literacy measure	Form	Approximate time taken	Health Literacy categorisation
Ratings of understanding (continued)	**Single-Item Literacy Screener**[151] (SILS)	Single question: ‘How often do you need to have someone help you when you read instructions, pamphlets or other written material from your doctor or pharmacy’, Answered on a 5-point Likert scale from ‘1-Never to ‘5-Always’	<1 minute	<3: Adequate ≥3: Limited
	Two-Item Literacy Screener[156] (TILS)	Two questions: What was the last (educational) grade you completed? Can you estimate your reading ability with one of the following: ‘I frequently read complete books’, ‘I read the newspaper’, ‘I occasionally need help with the newspaper’, or ‘I frequently need help with the newspaper’ Scored from -4 to +5	<1 minute	Sensitivity/specificity of different cut-off points was tested. Use of TILS>1 to indicate limited health literacy is suggested.

2.2.1.3 Health literacy and health disparities

The association between low health literacy and low SES has led to investigation of health literacy as a mediator between aspects of low SES and poorer health outcomes, and therefore a mechanism by which health disparities are promoted (Figure 2-2). A 2015 systematic review of studies investigating this association included 35 studies, most of which concerned the role of health literacy in promoting racial disparities in the USA.[157] Overall, evidence for an effect of health literacy in promoting inequity was limited. However, two studies from the USA (where non-white ethnicity has strong associations with low SES[17]) reported that health literacy appeared to mediate the association between non-white ethnicity or education [158, 159] with health status. Another study of 395 patients with diabetes used STOFHLA to test the association between low educational level and blood sugar control in diabetes using mediation analysis by Structural Equation Modelling (SEM).[160] A significant mediating effect of health literacy was reported. None of these studies included CKD populations.

Distinguishing between health literacy as a *feature* of patients with low SES and poor health outcomes and health literacy as a factor on the *causative pathway* between low SES and poor health outcomes is important if health literacy research is to inform healthcare policy. Interventions to improve understanding among those with low health literacy are more difficult to justify if health literacy is not shown to have proven associations with outcome. Chapter 6 investigates the potential mediating effect of health literacy in the association between low SES and outcomes in CKD.

2.2.1.4 Limited health literacy prevalence, associations and outcomes in non-CKD populations

A 2005 systematic review of this area, which aimed to establish the prevalence of limited health literacy found 85 studies in various health or healthcare settings.[15] The calculated pooled prevalence of limited health literacy among the 31,129 patients studied was 26% (95% CI: 22-29%), but variation in health literacy measure, setting and non-random sampling methods limited the reliability of prevalence estimates. No studies included CKD populations. Limited health literacy was associated with reduced level of education, older age, non-white ethnicity, and lower income. A European study of health literacy which included 8000 participants from the general population of eight countries found that 47.6% had limited health literacy,[161] associated with low SES. A large Danish study (n=29,473) found that people with long-term conditions were more likely to have health literacy problems.[162] In England, the presence of a long-term condition is associated with low numeracy.[145]

In 2011, an updated systematic review of the effect of low health literacy on health outcomes [16] identified 96 studies and found consistent associations between low health literacy and hospitalisations, use of emergency care, reduced use of preventative care such as mammography and influenza vaccinations, and reduced ability to administer medications. Elderly patients with low health literacy were found to have reduced health status and increased mortality. A UK study of 7857 older adults reported similar findings of increased mortality in those with reduced health literacy.[163]

2.2.1.5 Prevalence and associations of limited health literacy in CKD populations

By comparison, evidence of the prevalence of limited health literacy and its association with patient factors and outcomes in CKD is lacking. A 2012 systematic review of the prevalence and associations of limited health literacy in CKD patients[18] identified six studies. In total, 1,405 patients were studied, the majority being maintenance haemodialysis patients. All studies were from the USA. From the prevalence estimates in individual studies, prevalence values were calculated by meta-analysis, giving a pooled prevalence of 22.7% (95% CI: 20.6-24.8%). Limited health literacy was consistently and independently associated with low SES. Some outcome measures were tested: one study associated limited health literacy with mortality in 480 haemodialysis patients.[164] This review identified the need for studies of patients with pre-end-stage CKD, and studies from outside the USA. This review is updated in Chapter 3, along with a systematic review of associations between limited health literacy and outcomes in CKD.

2.3 Disease and treatment burden and the cumulative complexity model of disease

Sections 2.1 and 2.2 describe how SES and health literacy may interact to affect patients' treatment and outcomes. From available evidence, a further interaction also exists between these concepts and multimorbidity. This is illustrated in the cumulative complexity model of disease (Shippee et al),[146] which considers the interplay between SES, comorbidity, health literacy and other patient factors. Because of the known associations between CKD and multimorbidity,[165] this model of chronic disease is especially relevant to people with CKD.

The model (Figure 2-5) describes competing factors contributing to patients' success or failure in managing their health. The concept of patient 'workload' describes the demands put upon patients to perform tasks. These include the demands of treatment, such as organising and taking medications, as well as activities required to succeed in general life such as employment and family activities. The individual elements of total workload can vary over time, for instance, the number of hospital appointments or medications could increase or decrease.

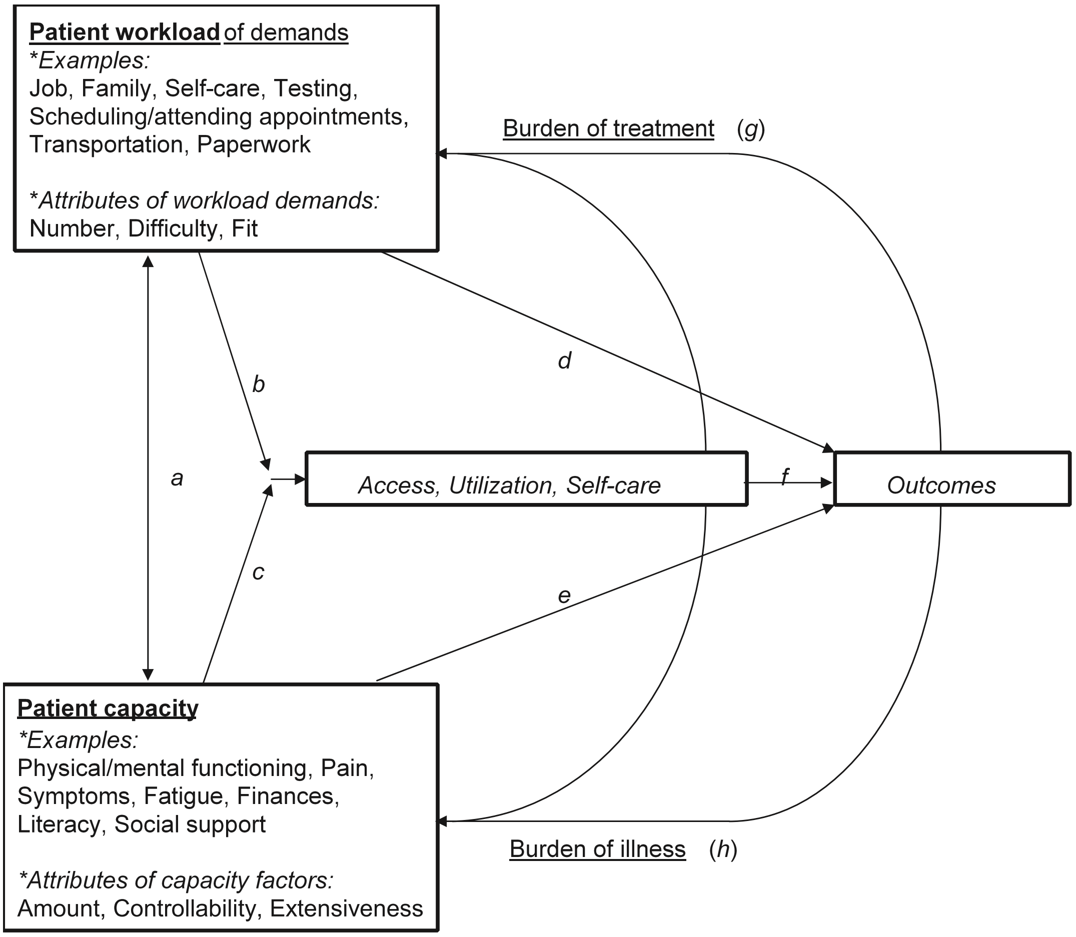


Figure 2-5: **The cumulative complexity model**

From Shippee et al, 2012[146]

Individuals' resources to perform this workload are defined in the model as patient 'capacity'. Capacity is influenced by patients' social situation (eg: increased by stronger social networks), by symptoms of disease (eg: reduced capacity to perform tasks because of pain, stress or fatigue), and by personal attributes or skills (eg: improved by better literacy, language or communication skills). Increasing illness and the associated increase in treatment can therefore simultaneously increase workload (via 'burden of treatment') and reduce capacity (through 'burden of disease').

For the patient with progressive CKD, workload and capacity would be expected to change at different points in the patient pathway (Figure 1-4). Workload would be expected to be high when a patient is required to attend thrice-weekly dialysis sessions, but may fall after successful transplantation. Capacity, which is influenced by disease symptoms and function, may also change. Studies measuring health-related Quality of Life (QoL) show progressive reductions in (among other domains) physical functioning, energy and vitality with CKD progression - functions that would be expected to influence capacity.[166] Compared to those with earlier CKD, dialysis patients have reduced QoL including physical function,[61] whereas transplant recipients long after transplantation report levels of QoL similar to population controls.[5]

The pathways marked *a-f* in Figure 2-5 illustrate the hypothesis that capacity and workload interact to influence disease treatment and self-care. In situations where workload exceeds capacity, negative disease outcomes may ensue, leading to increased morbidity, and further increasing the burden of disease and treatment. Within this model, examples of patient attributes that improve capacity include finances and social capital (related to SES, Section 2.1) and literacy or 'health literacy' (Section 2.2).

The principles of disease and treatment burden and the cumulative complexity model are used to inform the discussion of the potential effects of health literacy in CKD in Chapters 3-6.

2.4 Key research questions and thesis components

Patients with CKD are required to navigate complex pathways of disease and treatment. There is potential for SES, health literacy and comorbidity to interact to influence individuals' success or failure with decision-making and disease management. However, there are several areas where further knowledge of health literacy in CKD is required, in order to inform future research and policy. The key research questions for the remainder of this thesis are:

- What is the prevalence of limited health literacy among people with CKD, and does this differ between patients at different stages of disease and treatment (including between dialysis and transplant populations)?
- What are the demographic and socioeconomic associations with limited health literacy among people with CKD?
- What associations can be identified between limited health literacy and clinical outcomes?
- Do the measured relationships between SES, health literacy and outcomes support the hypothesis of health literacy as a mediator between SES and outcomes?

This thesis attempts to address these questions by systematic review of the current literature and by novel research of a large UK cohort of patients from the ATTOM study.

The components of the remainder of this thesis are as follows:

Chapter 3	Systematic reviews: health literacy prevalence, associations and outcomes in CKD: 1. A systematic review of the prevalence and associations of limited health literacy in chronic kidney disease, (updated from Fraser *et al.* 2012.[18]) 2. A systematic review of limited health literacy and clinical outcomes
Chapter 4	The Access to Transplant and Transplant Outcome Measures (ATTOM) study: methods and introduction
Chapter 5	Limited health literacy prevalence and associations: analysis of baseline data from the ATTOM study
Chapter 6	Limited health literacy and patient outcomes: analysis of prospective data from the ATTOM study
Chapter 7	Conclusions

Chapter 3: Systematic reviews: limited health literacy prevalence, associations and outcomes in CKD

3.1 Introduction

This chapter reviews current knowledge of the prevalence and associations of limited health literacy in CKD and the association between limited health literacy and clinical outcomes in CKD. The first systematic review of health literacy prevalence and associations is an update of Fraser et al,[18] and was performed because of a rapid expansion in the available literature since its publication in 2012. The second is a systematic review of health literacy and clinical outcomes in CKD, a subject not addressed in peer reviewed publication before. The two reviews shared some methodology, which is explained in the shared methods section 3.2. Unless otherwise stated, DT performed the analyses described in the methods sections.

The results in section 3.3 have been published as:

Taylor DM, Fraser SDS, Bradley JA*, et al.* A Systematic Review of the Prevalence and Associations of Limited Health Literacy in CKD. *Clin J Am Soc Nephrol* 2017.

and the results in section 3.4 as:

Taylor DM, Fraser SDS, Oniscu G, et al. Health literacy and patient outcomes in chronic kidney disease: a systematic review. Nephrology Dialysis Transplantation 2017.

This published papers are included in Appendix F.

Additional material relating to the systematic reviews in this chapter is in Appendix B

3.2 Search strategy and shared methods

The review protocols were registered with the international prospective register of systematic reviews: http://www.crd.york.ac.uk/PROSPERO , registration numbers D42016036742 (health literacy prevalence and associations) and CRD42016049172 (health literacy and clinical outcomes).

The search strategy (Appendix B) was developed by DT, with assistance from Paula Sands, Librarian at the Health Services Library of the University of Southampton. Development of this search strategy was informed by the strategy used in the 2012 review,[18] from a Cochrane systematic review protocol for health literacy interventions in CKD[19] and from review articles of health literacy measurement tools.[147-149, 152, 167-169] Both reviews used these search terms. This was possible because the search strategy included a combination of health literacy and CKD specific terms without reference to prevalence, associations or outcomes.

Electronic databases were searched by DT in August 2016. The databases used were Medline (1996 onwards), Embase (1980 onwards), OvidFullText (including PsychArticles, 1980 onwards), Health Management Information Consortium (1979 onwards), CINAHL (1981 onwards) and Psychinfo (1806 onwards). In addition to database searches, reference lists from articles included in this review and from other review articles were hand-searched. 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 these database searches. In addition to database searches, abstract archives 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'.

Two reviewers (DT and Dr. Simon Fraser, SF) independently assessed references for inclusion by the inclusion criteria for each review (Sections 3.3.1 and 3.4.1). For each review, 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 if required to establish if a study should be included, or to request additional data to increase the quality of the review.

Study quality was scored independently by DT and SF using an agreed scoring system, developed with reference to a review of tools for assessing the quality of observational studies.[170] Studies were assigned scores for sample size, setting, recruitment methods, and potential for unrecognized confounding of results. Scores were combined to indicate study quality and used to inform grading of studies as 'low', 'moderate' or 'high' quality. However, this scoring acted as a guide only and grading of studies was decided by discussion between the two reviewers.

3.3 Systematic review of limited health literacy prevalence and associations in chronic kidney disease

This systematic review of health literacy prevalence and associations in CKD includes a publication from the ATTOM study, results from which are presented fully in Chapter 5:.

3.3.1 Further methods

Search results from December 2011 to August 2016 were included in this updated review, along with studies included in the 2012 review.[18] DT and SF independently assessed the references for inclusion by three criteria:

1. At least 50 adults over 18 with CKD were included
2. The study used a validated measure to quantitatively describe health literacy
3. The study reported the prevalence of limited health literacy, or data from which this could be derived.

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. Unpublished studies available as abstracts from nephrology and health literacy conferences are reported in a sensitivity analysis (Appendix B.2).

For each study, the prevalence of limited health literacy, number of unique participants, study methods and demographics of participants were recorded. Meta-analysis was performed with subgroup analysis by CKD treatment stage (Non-dialysis CKD; Dialysis; Transplant) and by health literacy measure. Results were presented as Forest plots, with 95% confidence intervals for each prevalence value and for the pooled prevalence of limited health literacy. I^2 statistics were calculated to measure the degree of heterogeneity between studies and subgroups. A random-effects model was used because significant heterogeneity was present in the prevalence of limited health literacy in the results of the 2012 review[171], so was expected in the results of the present review. Univariate meta-regression was performed for continuous variables, which included the proportion of patients with non-white ethnicity and the age of participants (mean or median). If data on treatment stage, age or ethnicity were unavailable, studies were excluded from each analysis.

For studies where more than one validated health literacy measure was used, scores from STOFHLA (Short Test of Functional Health Literacy in Adults) are presented here because of its use as a reference measure to validate health literacy screening tools.[152, 156, 172] Analyses were then repeated using scores from other measures to establish if this altered the overall results. Socio-demographic characteristics significantly associated with limited health literacy were summarized, with covariates included in multivariate models, to identify independent associations. Statistical significance within studies was defined by individual study methods. A p-value of <0.05 was selected *a priori* to define statistical significance for meta-analysis and meta-regression. Analyses were performed using the user-written commands ‘metaprop’ and ‘metareg’ in Stata 12 (StataCorp LP, USA).

3.3.2 Results

Figure 3-1 shows the study selection process, which identified 433 unique studies, 15 of which met the inclusion criteria,[152, 156, 173-185] with full agreement between the two reviewers. Table 3-1 summarises the 15 new studies in addition to five studies included in the 2012 review.[164, 186-189] All 20 studies are included in the following description and analysis.

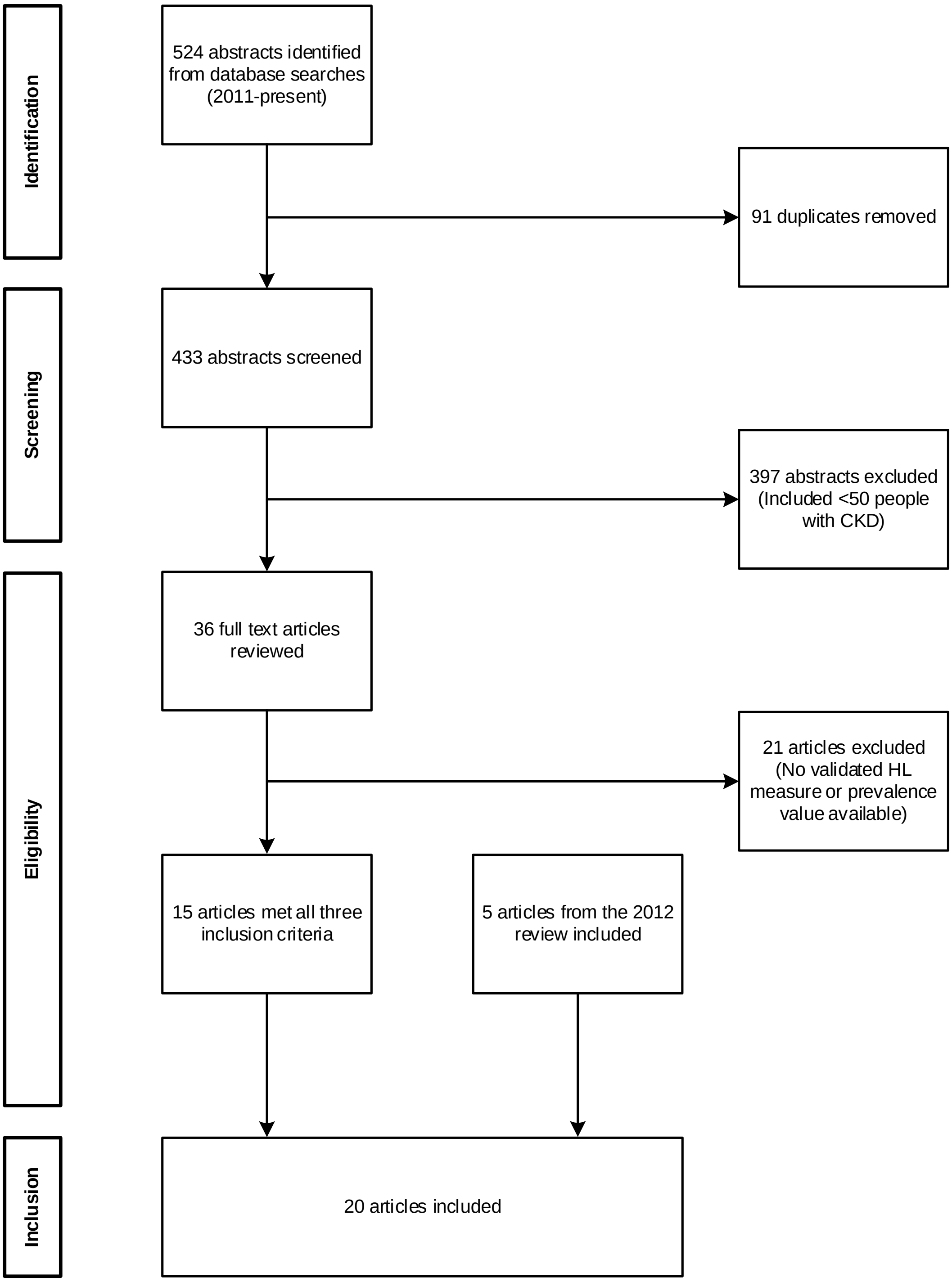


Figure 3-1: Study selection process: Systematic review of limited health literacy prevalence and associations in CKD

CKD: Chronic Kidney Disease; HL: Health literacy.

Table 3-1: Characteristics of studies included: Systematic review of limited health literacy prevalence and associations in CKD

Outcome variables are listed only if statistical models included health literacy as an exposure variable. * Studies included in Fraser 2012 review. α Frequencies from personal communication with the authors.

CKD- Chronic Kidney Disease; HL-Health Literacy; HD- Haemodialysis; PD- Peritoneal Dialysis; BP-Blood Pressure; BMI- Body Mass Index; PVD- Peripheral Vascular Disease; -Living-donor recipient; DDR- deceased-donor recipient; AKI- Acute Kidney Injury; MDRD: Modification of Diet in Renal Disease; ED- Emergency Department; LDL- Low density lipoprotein; SES- Socioeconomic status

Study Year Country	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Design	Setting & recruitment method	Participants	Exclusion criteria	Health literacy measure	Outcome variables tested	Prevalence of limited health literacy (%)
Adeseun [173] 2012 USA	72	[52]	68	Incident Dialysis (HD or PD)	Examine relationship between health literacy and cardiovascular disease risk factors	Cohort (baseline data)	Adults from transplant evaluation clinics taking part in the Dialysis Heart and Bone Study.	100% with limited health literacy were black, compared to 50% of those with adequate health literacy	Previous coronary revascularization, cardiac devices or weight >350lbs	STOFHLA	BP, lipid profile, waist-to-hip ratio, BMI, Tobacco use	21
Boulware [174] 2013 USA	130	60	40	Non-dialysis CKD 3-5	Compare the effectiveness of educational interventions on pre-emptive living-donor kidney transplantation	Cohort (baseline data)	Nephrology clinics	46% white 47% black <1% Hispanic	<18, >70, Non-English speaking, previous transplant, cancer heart failure, severe liver disease, PVD, HIV, unstable coronary artery disease.	REALM	-	25
Brice [156] 2014 USA	227	-	-	Prevalent HD	Validate TILS and SILS against STOFHLA	Cross-sectional	Adults from 7 HD centres	English (96%) and Spanish speakers (4%)	<18, Unable to speak English or Spanish. 'Mental impairment' defined by dialysis staff. Poor vision.	STOFHLA, SILS and TILS (English or Spanish)	-	45 (STOFHLA) 22 (SILS)

Study Year Country	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Design	Setting & recruitment method	Participants	Exclusion criteria	Health literacy measure	Outcome variables tested	Prevalence of limited health literacy (%)
Cavanaugh 1 *[164] 2010 USA	480	62	56	Incident HD	Measure the prevalence and associations of limited health literacy and risk of all-cause mortality	Cohort	Adults 'eligible for a patient education program' from 77 Dialysis units. Health literacy measured if low literacy was suspected by case manager.	52% white 50% Diabetic	<18; Non-permanent dialysis patients, Known cognitive impairment, Non-English speakers, Nursing home residents.	REALM	Mortality	32
Cavanaugh 2 [152] 2015 USA	143	[52]	51	Prevalent HD	Validate BHLS against REALM and STOFHLA	Cross-sectional	Adults from 4 dialysis units	73% black.	<18. >80. Dialysis initiation <1 month. Non-English speakers. Cognitive impairment	BHLS (0-15) REALM and STOFHLA	-	23 (BHLS) 27 (REALM) 8 (STOFHLA)
Dageforde 1 [175] 2014 USA	255	[48]	64	Incident Transplant	Compare health literacy between living- and deceased-donor kidney transplant recipients and living kidney donors	Retrospective chart review	Transplant recipients and donors at single transplant centre surveyed for health literacy preoperatively	65% white LDR (n=103) DDR (n=152)	<18; No recorded answer to BHLS	BHLS (0-15)	Donor type, Education and demographics	12 (LDRs: 9%; DDRs: 14%)
Dageforde 2 [176] 2015 USA	104	[53]	61	Dialysis (n=14) and non-dialysis CKD (n=90)	Characteristics of attenders vs absentees for kidney transplant evaluation appointments	Cross-sectional	Convenience sample of 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	23 (14% dialysis; 24% CKD)
Devraj [177] 2015 USA	150	45% over 60	47	Non-dialysis CKD1-4	Relationship between health literacy and eGFR	Cross-sectional	Adults attending follow-up nephrology outpatients 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)	63

Study Year Country	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Design	Setting & recruitment method	Participants	Exclusion criteria	Health literacy measure	Outcome variables tested	Prevalence of limited health literacy (%)
Foster [178] 2011 USA	238	[58]	54	Prevalent Dialysis (HD or PD)	Assess disaster preparedness in dialysis patients	Cross-sectional	Adults approached during dialysis at 6 dialysis units	57% black 6% Spanish-speaking, 94% English Speaking	<18, unable to understand consent process	STOFHLA (English or Spanish)	Disaster preparedness	49.5
Gordon* [186] 2011 USA	124	[47]	57	Prevalent Transplant	Relationship between health literacy, transplant knowledge and graft function	Cross-sectional	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	Demographics and graft function	9
Green* [187] 2011 USA	260	64	57	Prevalent HD	Describe prevalence and associations of limited health literacy	Cohort (baseline data)	Patients from 9 dialysis units included in an RCT of strategies for managing pain, sexual dysfunction and depression	40% black	<18, less than thrice-weekly dialysis, non-English Speakers, Cognitive impairment, considering switch to PD or transplantation	REALM	Demographics, SES, Comorbidity	16
Grubbs* [188] 2009 USA	62	[52]	66	Prevalent HD	Association of poor health literacy with access to transplantation	Cross-sectional	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	Referral for transplant evaluation, wait-listing or transplantation	32
McNaughton [179] 2014 USA	851[α]	55	57	CKD3-5, including dialysis or transplant if eGFR<60ml/min/1.73m^2	Relationship between limited health literacy and BP at ED presentation	Cross-sectional	Adults attending ED at a large quaternary hospital screened for health literacy as part of admission nursing assessment.	Study included 31,902 patients, of whom 851 (3%) had kidney disease. 60% white	<18; Nursing assessment or health literacy measure not completed, Admitted with pre-eclampsia or alcohol withdrawal.	BHLS (0-15)	BP at hospital presentation (in all ED attenders)	26[α]

Study Year Country	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Design	Setting & recruitment method	Participants	Exclusion criteria	Health literacy measure	Outcome variables tested	Prevalence of limited health literacy (%)
Miller-Matero [180] 2015 USA	95	-	-	Referred for transplantation (dialysis or advanced CKD)	Assess health literacy of patients referred for solid-organ transplantation	Cross-sectional	Patients considered for solid organ transplantation at a single centre.	-	-	REALM	Demographics, cognitive impairment, reading ability, numeracy (in all organ transplant recipients)	37.8
Ricardo [181] 2014 USA	2340	[58]	54	Non-dialysis CKD1-4	Association of limited health literacy with kidney function and CV risk factors	Cross-sectional	Adults with CKD recruited from 7 clinical centres.	52% white 48% black	<21 or >74 years; Polycystic Kidney [181]Disease; Hispanic Ethnicity	STOFHLA	eGFR (MDRD formula), BP, LDL cholesterol <100mg/dL, HbA1c <7%, self-reported CV disease	16 (black 28%; white 5%)
Robinson [182] 2015 USA	170	[50]	59	Prevalent Transplant	Validate a sun-protection education program	RCT (baseline data)	Adults from 2 transplant programs	35% black; 28% Hispanic; 36% white	<2 or >24 months after transplant; Non- Spanish speakers; <18 or >70; poor vision; ethnicity other than black, white or Hispanic	STOFHLA (English or Spanish)	-	36 (black 58%; Hispanic 54%; white 0%)
Taylor [183] 2015 UK	5520	54	62	Incident Dialysis (HD or PD), Incident Transplant and Transplant wait-listed (Prevalent dialysis- and non-dialysis CKD)	Describe prevalence and associations of limited health literacy	Cohort (baseline data)	Adults approached for notes review and survey from all 71 UK renal units	Representative nationwide sample. 79% white. Non-dialysis CKD patients were all pre-emptively wait-listed for transplant	<18 or >75 years or unable to provide informed consent.	SILS	Demographics, SES, Comorbidity	16 (Dialysis 18%; CKD Wait-listed 9%; Incident Transplant 12%)

Study Year Country	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Design	Setting & recruitment method	Participants	Exclusion criteria	Health literacy measure	Outcome variables tested	Prevalence of limited health literacy (%)
Weng [184] 2013 USA	252	[55]	60	Prevalent Transplant	Prevalence and correlates of medication non-adherence	Cross-sectional	Adults approached during a transplant clinic visit at a single centre. Offered $15	58% white 27% black Median 2.9 years post-transplant	<6 months post-transplant, <18, Non-English speakers, Unable to consent. Dual organ transplant.	STOFHLA	Medication non-adherence	2.4
Wright* [189] 2011 USA	401	58	53	Non-dialysis CKD1-5	Measure awareness and knowledge of CKD to develop a CKD knowledge survey	Cross-sectional	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	Kidney disease knowledge	18
Wright-Nunes [185] 2013 USA	154 (after excluding 401 from Wright)	58	54	Non-dialysis CKD1-5	Assess feasibility and impact of a physician-delivered education tool to increase CKD knowledge	Clinical trial, (baseline data)	Adults at single centre asked to complete a survey (written or read aloud). Offered monetary compensation.	77% white, 78% CKD3-5.	<18, Non-English speakers, kidney transplant or dialysis, vision or cognitive impairment	REALM	-	22

Of 20 studies, 13 were cross-sectional surveys, five used baseline data from cohort studies and two used baseline data from clinical trials. One study presented UK data,[183] all others reported from the USA. Study quality was graded as 'low' for 15 studies and 'moderate' for five studies.[164, 181-183, 186]

In total, 12,324 patients were studied, including 1,327 patients included in the 2012 review. This included 3,529 patients with non-dialysis CKD from seven studies, 5,289 dialysis patients from ten studies, and 2,560 transplant patients from five studies. Five studies included patients from multiple treatment stages. The prevalence of limited health literacy by treatment stage was not available for 946 patients from two studies,[179, 180] even after communication with authors. Studies included a median of 198.5 patients (IQR: 128.5 to 260).

One study included living kidney donors,[175] and one included recipients of solid organ transplants of different types[180] in addition to patients with CKD; subgroup information was available from published data. One study[179] measured health literacy in 46,000 emergency department attendees, including 851 with CKD.[179] The authors provided data on this subgroup by personal communication.

Table 3-2 summarises the health literacy measures and definitions of limited health literacy used in studies included in this review.

Table 3-2: Health literacy measures used: Systematic review of limited health literacy prevalence and associations in CKD

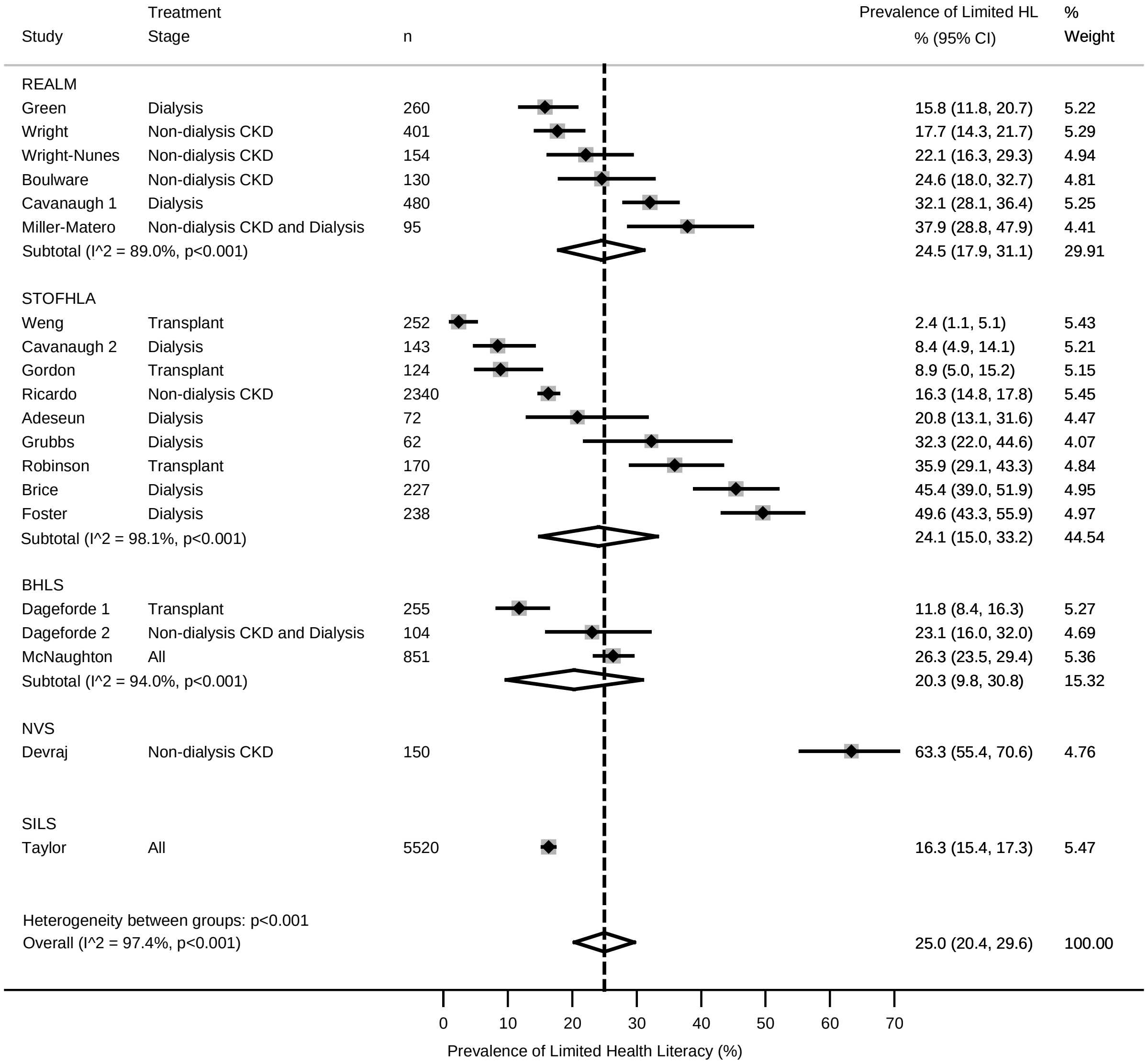
Health literacy measure	Number of studies using measure (%)	Form	Approximate time taken	Health literacy categorization
Short Test of Functional Health Literacy in Adults (STOFHLA)	9 (45) (3 studies used both English and Spanish versions)	36 reading comprehension items- select from four choices to replace missing words in text (modified Cloze procedure)	12 minutes	0-22 Limited 23-36: Adequate
Rapid Estimate of Adult Literacy in Medicine (REALM)	6 (30)	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)	1 (5)	69 kidney transplant-related terms tested for pronunciation accuracy	3 minutes	Not clearly defined
Brief Health Literacy Screen (BHLS)	4 (20)	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[190]	<1 minute	3-8 (or 0-5): Lower 9-14 (or 6-12): Moderate/Higher (<10/15 or <6/12 indicates limited health literacy)
Newest Vital Sign (NVS)	1 (5)	Six-item assessment of reading comprehension from an ice-cream nutrition label	6 minutes maximum (average 2.9 minutes)[144]	0-1: High likelihood marginal/inadequate 2-3: Possible marginal/inadequate 4-6: Adequate (Score <4 indicates limited health literacy[177])
Single-Item Literacy Screener (SILS)	2 (10) (1 used English and Spanish versions)	'How often do you need to have someone help you when you read instructions, pamphlets or other written material from your doctor or pharmacy', answered on a 5-point Likert scale from '1-Never to '5-Always'	<1 minute	<3: Adequate ≥3: Limited
Two-Item Literacy Screener (TILS)	1 (5) (English or Spanish)	Two questions: What was the last (educational) grade you completed? Can you estimate your reading ability with one of the following: 'I frequently read complete books', 'I read the newspaper', 'I occasionally need help with the newspaper', or 'I frequently need help with the newspaper' Scored from -4 to +5	<1 minute	Sensitivity/specificity of different cut-off points was tested. Use of TILS>1 to indicate limited health literacy is suggested.

One study included all emergency department attendees[179] and one aimed to approach all eligible patients UK-wide.[183] Two studies surveyed patients from clinical trials whose primary objective was unrelated to health literacy.[173, 187] All others recruited from clinical environments without efforts to obtain a sample representative of a target CKD population. Two studies surveyed CKD patients at transplant assessment clinics,[176, 180] while one excluded patients listed for transplant.[187] Three studies reported offering a monetary gift to participants.[184, 185, 189] At least 11 studies excluded patients with cognitive impairment. One study included patients deemed suitable for an educational intervention.[164] Six studies specified an upper limit for age, ranging from 74 to 80 years.[152, 174, 181-183, 188]

Ethnicity data were unavailable for one study (total 95 patients),[180] and age data for two studies (total 322 patients).[156, 180] From the remaining data, the median proportion of participants of non-white ethnicity was 48% (IQR: 23 to 64%) and mean or median age ranged from 47 to 72 years. In some US studies, the majority of study participants had black ethnicity.[152, 178, 188] One study excluded patients with Hispanic ethnicity.[181] Twelve studies included only English speakers. Three studies included Spanish speakers, and used health literacy measures translated into Spanish.[156, 178, 182]

The median prevalence of limited health literacy by study was 23% (IQR: 16 to 33%). The overall pooled prevalence of limited health literacy was 25% (95% CI: 20-30%). A high degree of heterogeneity was present between studies (I^2 =97.4%).

Figure 3-2 shows a Forest plot of the prevalence of limited health literacy in all 20 studies with subgroup analysis by health literacy measure.



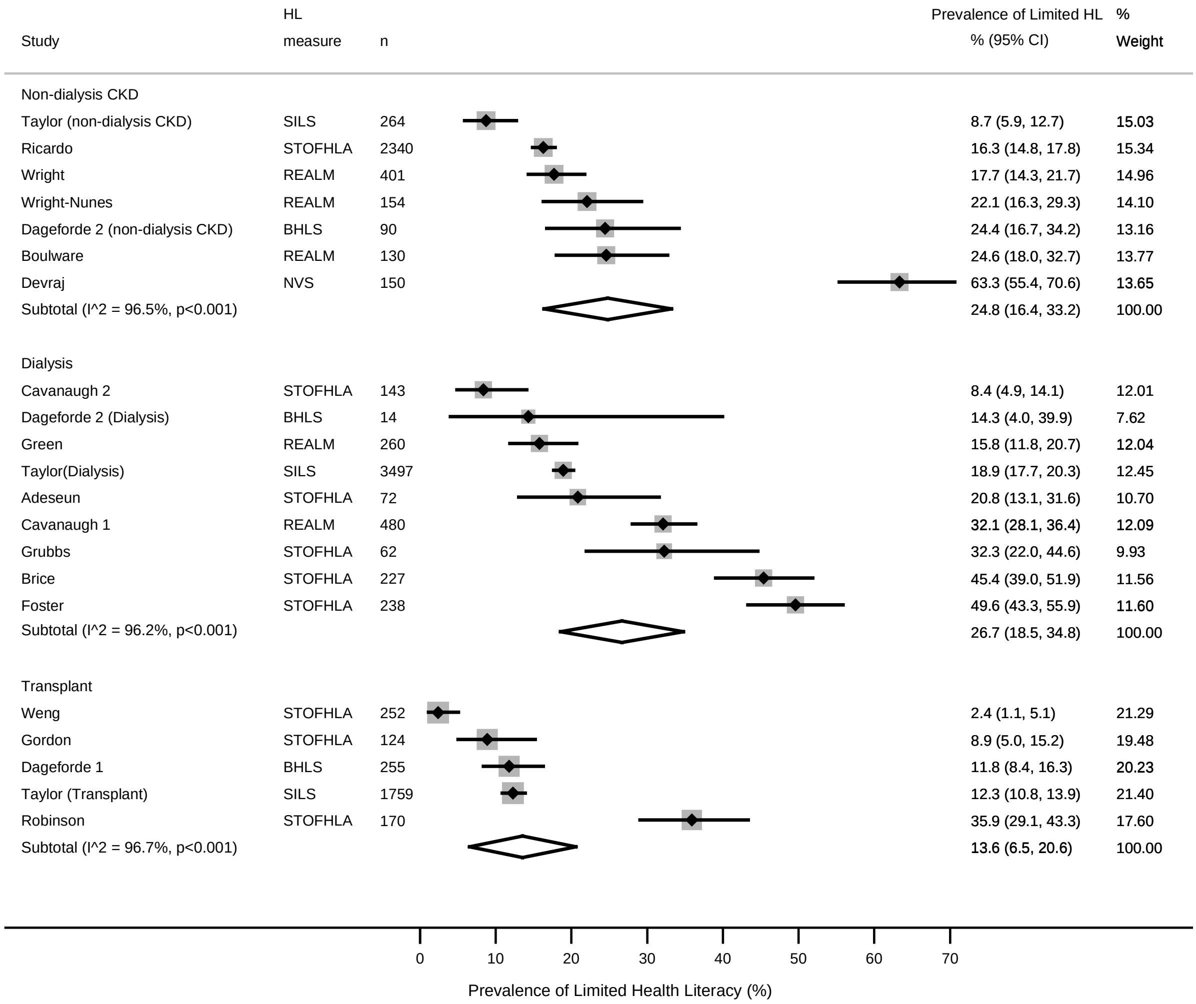
Study	Treatment Stage	n	Prevalence of Limited HL % (95% CI)	% Weight
REALM				
Green	Dialysis	260	15.8 (11.8, 20.7)	5.22
Wright	Non-dialysis CKD	401	17.7 (14.3, 21.7)	5.29
Wright-Nunes	Non-dialysis CKD	154	22.1 (16.3, 29.3)	4.94
Boulware	Non-dialysis CKD	130	24.6 (18.0, 32.7)	4.81
Cavanaugh 1	Dialysis	480	32.1 (28.1, 36.4)	5.25
Miller-Matero	Non-dialysis CKD and Dialysis	95	37.9 (28.8, 47.9)	4.41
Subtotal (I^2 = 89.0%, p<0.001)			24.5 (17.9, 31.1)	29.91
STOFHLA				
Weng	Transplant	252	2.4 (1.1, 5.1)	5.43
Cavanaugh 2	Dialysis	143	8.4 (4.9, 14.1)	5.21
Gordon	Transplant	124	8.9 (5.0, 15.2)	5.15
Ricardo	Non-dialysis CKD	2340	16.3 (14.8, 17.8)	5.45
Adeseun	Dialysis	72	20.8 (13.1, 31.6)	4.47
Grubbs	Dialysis	62	32.3 (22.0, 44.6)	4.07
Robinson	Transplant	170	35.9 (29.1, 43.3)	4.84
Brice	Dialysis	227	45.4 (39.0, 51.9)	4.95
Foster	Dialysis	238	49.6 (43.3, 55.9)	4.97
Subtotal (I^2 = 98.1%, p<0.001)			24.1 (15.0, 33.2)	44.54
BHLS				
Dageforde 1	Transplant	255	11.8 (8.4, 16.3)	5.27
Dageforde 2	Non-dialysis CKD and Dialysis	104	23.1 (16.0, 32.0)	4.69
McNaughton	All	851	26.3 (23.5, 29.4)	5.36
Subtotal (I^2 = 94.0%, p<0.001)			20.3 (9.8, 30.8)	15.32
NVS				
Devraj	Non-dialysis CKD	150	63.3 (55.4, 70.6)	4.76
SILS				
Taylor	All	5520	16.3 (15.4, 17.3)	5.47
Heterogeneity between groups: p<0.001				
Overall (I^2 = 97.4%, p<0.001)			25.0 (20.4, 29.6)	100.00

Figure 3-2: Forest plot showing the pooled prevalence of limited health literacy, grouped by the health literacy measure used.

Dashed reference line indicates pooled prevalence value. HL: Health literacy; CI: Confidence Interval; CKD: Chronic Kidney disease; BHLS: Brief Health Literacy Screener; REALM: Rapid Evaluation of Adult Literacy in Medicine; SILS: Single-Item Literacy Screener; STOFHLA: Short Test of Functional Health Literacy in Adults.

Studies using the Newest Vital Sign (NVS) and Single-Item Literacy Screener (SILS) reported significantly different prevalence values, but only one study used each measure.[177, 183] These prevalence values contributed to the significant overall heterogeneity in limited health literacy prevalence between studies using different measures (p<0.001). However, when studies using REALM (Rapid Estimate of Adult Literacy in Medicine), STOFHLA and BHLS (Brief Health Literacy Screen) were compared alone, no significant between-group heterogeneity was detected (p=0.8).

Figure 3-3 shows sub-group analysis by CKD treatment stage, excluding two studies where subgroup information was unavailable.[179, 180] The pooled prevalence of limited health literacy was 25% (95% CI: 16-33%) among patients with non-dialysis CKD, 27% (95% CI: 19-35%) among dialysis patients, and 14% (95% CI: 7-21%) among transplant patients. Overall, there was significant between-group heterogeneity (p=0.03), although this appears to be related to the lower prevalence of limited health literacy in transplant patients: when patients with non-dialysis CKD and dialysis patients were compared separately, no significant between-group heterogeneity was present (p=0.8).



Study	HL measure	n	Prevalence of Limited HL % (95% CI)	% Weight
Non-dialysis CKD				
Taylor (non-dialysis CKD)	SILS	264	8.7 (5.9, 12.7)	15.03
Ricardo	STOFHLA	2340	16.3 (14.8, 17.8)	15.34
Wright	REALM	401	17.7 (14.3, 21.7)	14.96
Wright-Nunes	REALM	154	22.1 (16.3, 29.3)	14.10
Dageforde 2 (non-dialysis CKD)	BHLS	90	24.4 (16.7, 34.2)	13.16
Boulware	REALM	130	24.6 (18.0, 32.7)	13.77
Devraj	NVS	150	63.3 (55.4, 70.6)	13.65
Subtotal (I^2 = 96.5%, p<0.001)			24.8 (16.4, 33.2)	100.00
Dialysis				
Cavanaugh 2	STOFHLA	143	8.4 (4.9, 14.1)	12.01
Dageforde 2 (Dialysis)	BHLS	14	14.3 (4.0, 39.9)	7.62
Green	REALM	260	15.8 (11.8, 20.7)	12.04
Taylor(Dialysis)	SILS	3497	18.9 (17.7, 20.3)	12.45
Adeseun	STOFHLA	72	20.8 (13.1, 31.6)	10.70
Cavanaugh 1	REALM	480	32.1 (28.1, 36.4)	12.09
Grubbs	STOFHLA	62	32.3 (22.0, 44.6)	9.93
Brice	STOFHLA	227	45.4 (39.0, 51.9)	11.56
Foster	STOFHLA	238	49.6 (43.3, 55.9)	11.60
Subtotal (I^2 = 96.2%, p<0.001)			26.7 (18.5, 34.8)	100.00
Transplant				
Weng	STOFHLA	252	2.4 (1.1, 5.1)	21.29
Gordon	STOFHLA	124	8.9 (5.0, 15.2)	19.48
Dageforde 1	BHLS	255	11.8 (8.4, 16.3)	20.23
Taylor (Transplant)	SILS	1759	12.3 (10.8, 13.9)	21.40
Robinson	STOFHLA	170	35.9 (29.1, 43.3)	17.60
Subtotal (I^2 = 96.7%, p<0.001)			13.6 (6.5, 20.6)	100.00

Figure 3-3: Forest plot showing the pooled prevalence of limited health literacy, grouped by CKD treatment stage

Two studies where treatment stage was not defined are not shown. HL: Health literacy; CI: Confidence Interval.

Univariate meta-regression analysis showed a significant association between the proportion of non-white participants in a study and the prevalence of limited health literacy (ß:0.35; 95% CI: 0.001,0.69; p=0.044). This equates to a 3.5% increase in the prevalence of limited health literacy for every 10% increase in the proportion of non-white participants. Average age of study participants was not significantly associated with the prevalence of limited health literacy (ß: 1.05; 95% CI: -0.5,2.6; p=0.4).

Two studies used multiple health literacy measures, reporting three limited health literacy prevalence values each.[152, 156] In the above analyses, results defined by STOFHLA were used for both studies. Repeated analyses using each of nine possible combinations of limited health literacy prevalence values did not lead to a change in the significance of the above results, except for meta-regression by proportion of non-white participants. In four of nine combinations, this association was no longer statistically significant. A further sensitivity analysis included 11 conference abstracts in addition to the 20 published papers included here. Analysis of results from all 31 studies showed a pooled prevalence of limited health literacy of 25%, and no change in the pattern of results as presented above. However, when abstracts were included, the significance of the association between proportion of non-white participants and limited health literacy prevalence increased (p=0.005).

Table 3-3 summarizes significant associations with limited health literacy and covariates included in multivariate models. A large variety of variables was tested. In ten studies which undertook multivariate analysis, the only demographic factors consistently and independently associated with limited health literacy were ethnicity,[164, 173, 187] and markers of lower SES including income[173, 186, 188] and lower educational level.[164, 175, 183, 186-188] Independent associations were also reported between limited health literacy and older age,[188] male gender,[164] lower English fluency,[183] individual comorbidities[177, 181] and higher comorbidity score.[183]

In patients with non-dialysis CKD, two studies reported independent associations between limited health literacy and lower eGFR.[177, 181] Limited health literacy was associated with deceased-donor transplantation (compared to living-donor) and transplantation after dialysis start (compared to pre-emptive).[183] One study reported an independent association between limited health literacy and mortality.[164]

Table 3-3: Summary of univariate and multivariate associations with limited health literacy: Systematic review of health literacy prevalence and associations in CKD

Markers indicate significant association with limited health literacy. Shading indicates covariates in multivariate models. *African-American, †Non-white; ‡Hispanic; § South Asian, Chinese.

		Demographics							Socioeconomic								Comorbidity											Biochemistry				Drugs			Dialysis					Transplant				Knowledge/education						
Univariate Associations		Older age	Male	Ethnicity	English Fluency	Veteran	Support person	Renal unit	Non-Employment	Lower income	Lower educational level	Non car ownership	Non-married	More children	Insurance	Other SES measure	Lower Physical Activity	Kidney disease duration	Higher comorbidity index	CV disease	Diabetes	BMI	Hypertension	Higher Blood Pressure	Hyperlipidaemia	Psychosis	Smoking	Lower eGFR	Proteinuria	Albumin	HbA1c	ACE/ARB	Insulin use	Aspirin	Dialysis initiation	Dialysis adequacy (Kt/V)	Fistula (compared to catheter)	Age at dialysis start	Dry Weight	Deceased-donor (vs live)	Non pre-emptive transplant	Time since transplant	Previous transplant	Lower objective knowledge	Lower percieved health	Kidney education resource use	Nephrologist care	Aware of diagnosis	Know someone with CKD	Increased mortality
Adenseun				• *						•	•																																							
Cavanaugh 1				• †							•		•																	•									•											•
Dageforde 1																																								•										
Devraj				• ‡						•	•				•																																			
Gordon										•	•		•																																					
Green				• *		•				•	•								•																		•													
Grubbs		•								•	•																																							
Ricardo		•		• †						•	•						•			•	•		•					•	•				•												•					
Taylor		•		• §	•				•		•		•	•					•							•														•	•									
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Multivariate Associations																																																		
Study	**Model**																																																	
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Cavanaugh 1	1	▨	▨ •	▨ • †							▨ •		▨								▨	▨								▨						▨														
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	2	▨	▨	▨				▨												▨ •	▨	▨		▨	▨		▨	▨			▨	▨	▨	▨	▨															
Taylor		▨	▨	▨	▨ •				▨ •		▨ •	▨ •							▨ •							▨ •																								
Wright		▨																										▨																▨ •		▨		▨	▨	

3.3.3 Discussion

This systematic review of literature published until mid-2016 demonstrates the significant expansion of health literacy research in CKD. Fifteen studies published since 2012 were identified, and 12,324 patients have now been studied, compared to 1,405 in the 2012 review by Fraser et al.[18] Geographical variation of studies remains limited: only one was from outside the USA. The pooled prevalence of limited health literacy in the present analysis was 25%, similar to 23% in the 2012 review. The six new studies of patients with non-dialysis CKD and four new studies of transplant patients allowed meta-analysis by patient group, confirming the reduced prevalence of limited health literacy among transplant patients, which has been reported in individual studies.[183] Four new studies used the BHLS, and comparison with studies using REALM and STOFHLA showed no significant difference in limited health literacy prevalence, increasing the confidence with which results can be compared between studies of CKD patients using these health literacy measures.

The lower prevalence of limited health literacy among kidney transplant patients has several possible explanations. Limited health literacy may directly impede effective clinician-patient communication, reducing the likelihood of clinically-suitable patients understanding the benefits of transplantation and pursuing it as a treatment option. Because of associations with low SES, limited health literacy has been implicated as a possible mediating factor in reducing access to transplantation. However, mechanisms by which low SES associates with reduced access to transplantation[191] are complex (and in the USA, include reduced access to immunosuppressant drugs.[133] The associations of both limited health literacy[183] and SES[114] with increased number of comorbidities and the severity of comorbidity add further complexity: patients with limited health literacy and low SES may in fact be less suitable for transplantation for clinical reasons. These complex associations warrant further investigation.

Studies which included a higher proportion of individuals of non-white ethnicity were significantly more likely to report a higher prevalence of limited health literacy. As 19 out of 20 studies were from the USA, non-white ethnicity represents patients with black American or Hispanic ethnicity. Non-white ethnicity in the USA has established, complex associations with low SES[17] and poorer health outcomes,[134] so this may represent confounding by SES and comorbidity. Although all three studies that reported independent associations between ethnicity and limited health literacy adjusted for SES,[164, 173, 187] only one adjusted for comorbidity (as presence or absence of diabetes).[164] Age of study participants did not appear to influence the prevalence of limited health literacy, though this analysis was limited by missing age data for two studies and the lack of a standard measure of average age (only mean *or* median was available).

Even after adjustment for treatment stage, health literacy measure, age or ethnicity, there was significant residual heterogeneity in the prevalence of limited health literacy between studies. Study methodology had potential to contribute to this heterogeneity. Sample size was mostly small (median 189). The majority of studies recruited patients by convenience in clinical environments, which may result in participation bias. Studies which included only patients who had been referred for transplantation (or excluded those who had been referred) are likely to be unrepresentative of the general dialysis population.[185, 187, 189] Patients with cognitive impairment or language difficulties may demonstrate a reduction in understanding and be falsely classified as having limited health literacy. Many studies excluded those with cognitive impairment for this reason. Doing so would be expected to result in an underestimate of the true prevalence of limited health literacy. The approach to patients whose first language is not English could also bias results. Some studies excluded non English-speakers, who would be more likely to have limited health literacy because of its association with non-white ethnicity and lower SES. Others used translated versions of health literacy measures to allow inclusion of non-English speakers. However, non-English versions of health literacy measures have not been validated extensively, and comparison of results between English and non-English versions is problematic because of inherent differences between English-speaking and non English-speaking populations.[192] Other studies used English health literacy measures for all participants, which could result in patients being falsely classified as having low health literacy because of poor understanding related to language.[175, 179, 180, 183]

The different health literacy measures used vary in their method of assessment and in the skills which are assessed. This limits comparability of results between studies. REALM and STOFHLA are direct assessments of pronunciation and reading comprehension, whereas the screening tools BHLS and SILS focus on patient’s perception of their level of understanding. It is reassuring that the BHLS produced similar prevalence estimates to REALM and STOFHLA in our meta-analysis, although health literacy screening tools have been shown in validation studies of CKD and other populations to lack sensitivity and specificity in detecting limited health literacy defined by REALM or STOFHLA.[151, 152, 156, 172] Screening tools benefit from short administration times, so are more practical for use in large-scale cohort studies or for screening in clinical practice. The NVS[144] is the only measure used here that assesses poor numeracy: a common characteristic of patients with CKD[193] and other chronic diseases[145] which may impair patients’ ability to dose medications, follow dietary advice and keep appointments.[194]

Systematic reviews of health literacy prevalence in other populations report similar findings. A 2005 review of US studies reported a pooled prevalence of 26% ‘low’ health literacy, associated with lower educational level, black ethnicity and older age.[15] A review of health literacy in patients with musculoskeletal diseases found between 7% and 42% low health literacy, associated with lower SES.[195]

This review benefits from a comprehensive search strategy using updated search terms. Eligibility criteria were clearly defined. Valuable communication was sought and received from many authors, enhancing the quality of the review. A sensitivity analysis, which included data from conference abstracts, identified no major differences in results. There are several limitations:

- Studies were of low or moderate quality because of small sample size, single centre samples and non-representative sampling methods.
- Studies using newer measures that measure multiple aspects of health literacy on separate scales,[196] but do not define limited health literacy could not be included.
- Most studies used cross-sectional data and the association of limited health literacy with increased mortality[164] could result in survivorship bias and an underestimate of limited health literacy prevalence in cross-sectional studies.
- Meta-regression to account for age and ethnicity differences between studies was especially limited by missing data, and multivariate meta-regression was not possible. However, a positive association was still shown between non-white ethnicity and limited health literacy prevalence, despite this lack of power.
- Ages of study participants were available as mean *or* median, limiting the reliability of meta-regression analysis by age and the power of this analysis to detect an association.
- One study showed a lower prevalence of limited health literacy among those listed for transplantation compared to incident dialysis patients,[183] but this association could not be investigated here because of the absence of consistent data on wait-listing status.

In summary, this review demonstrates that a quarter or more of CKD patients have limited health literacy, which is associated with markers of low SES, non-white ethnicity, and comorbidity. A lower prevalence of limited health literacy among transplanted patients compared to those on dialysis may suggest selection of patients with higher health literacy for transplantation. This is investigated in Chapters 4-6.

3.4 Systematic review of health literacy and patient outcomes in chronic kidney disease

3.4.1 Further methods

The full results of the searches detailed in section 3.2 were used in this review. DT and SF independently reviewed references by the following 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

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. In this review, results from conference abstracts are presented alongside those from published papers.

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 3-5.

Measures of effect for significant associations 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: DT and SF decided the final quality grading by discussion. Statistical significance was defined *a priori* as $p<0.05$, unless individual study methodology specified a lower threshold.

3.4.2 Results

Figure 3-4 shows the study selection process. Twenty-nine studies were eligible for inclusion,[164, 173, 176-178, 184, 186, 188-190, 197-215] summarised in Table 3-4 There was full agreement between the two reviewers as to which studies met the inclusion criteria. Thirteen published articles[164, 173, 176-178, 184, 186, 188, 189, 200, 203, 214, 215] and 16 conference abstracts[190, 197-199, 201, 202, 204-213] were included. Five were cohort studies (two published articles,[164 200] and three conference abstracts[190, 204, 212]); and 23 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 3-4).[190] All others reported exclusively on patients from the USA.

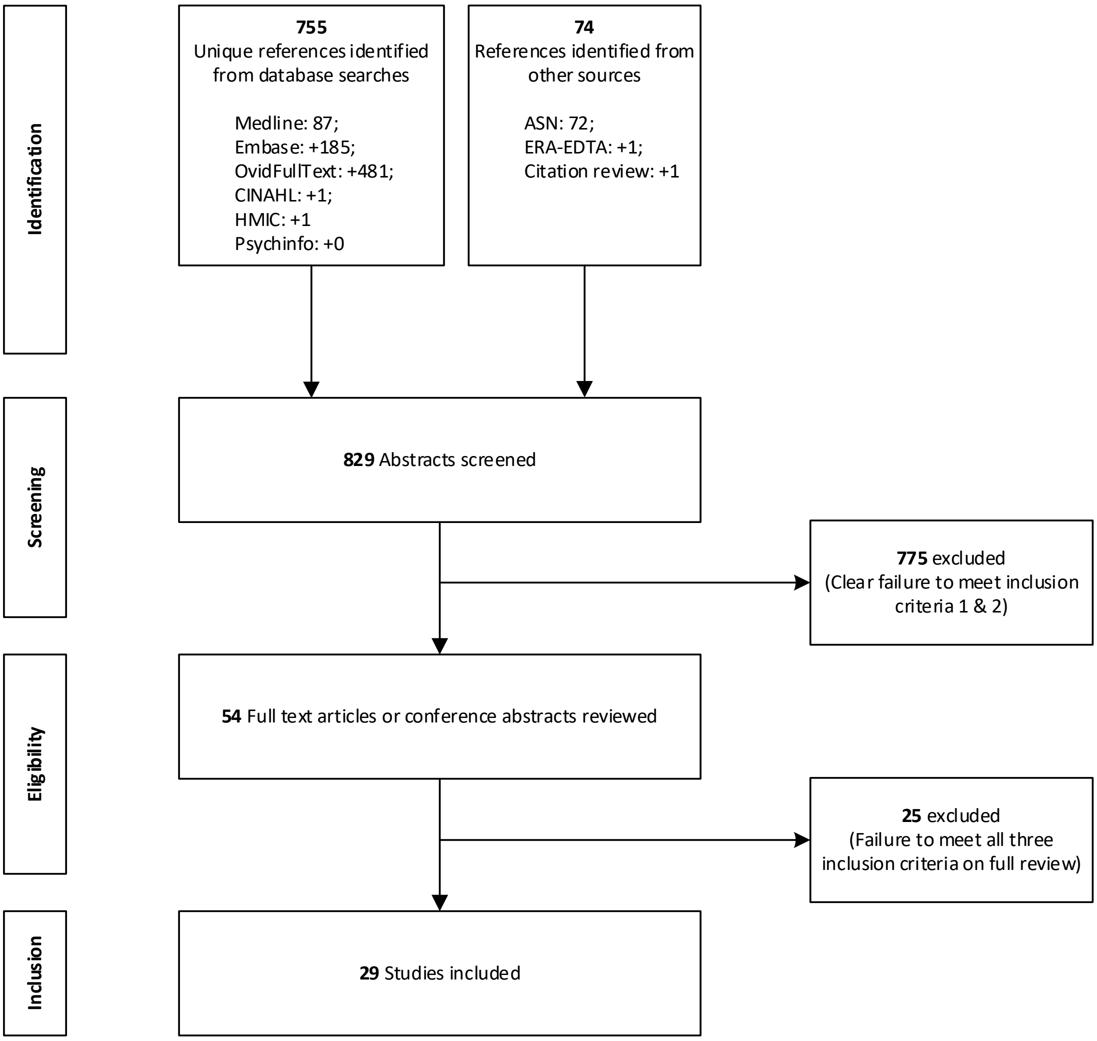

Figure 3-4: Study selection process: Systematic review of health literacy and clinical outcomes in CKD

Table 3-4: Summary characteristics of included studies: Systematic review of health literacy and clinical outcomes in CKD

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 Country	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 [164] 2010 USA	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 (laboratory values)
	Cavanaugh 2 [190] (abstract) 2015 USA	11,476	-	-	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 [200] 2013 USA	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 [204] (abstract) 2016 USA	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 [212] (abstract) 2016 USA	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 Country	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 [197] (abstract) 2015 USA	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 [173] 2012 USA	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 [198] (abstract) 2011 USA	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 [199] (abstract) 2010 International	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 [176] 2015 USA	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 [177] 2015 USA	150	45% over 60	47	Non-dialysis CKD1-4	Relationship between HL and eGFR	Adults attending follow-up nephrology outpatients 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 [178] 2011 USA	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 Country	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 [186] 2011 USA	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 [188] 2009 USA	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 [201] (abstract) 2005 USA	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 [202] (abstract) 2014 USA	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 [203] 2014 USA	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 [205] (abstract) 2015 USA	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	

	Study Year Country	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)	Posadas[206] (abstract) 2011 USA	83	-	43	Prevalent HD	Identify patient factors associated with dialysis catheter use	Single HD unit	-	None stated	STOFHLA	HD catheter use	-
	Puher[207] (abstract) 2014 USA	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[208] (abstract) 2016 USA	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[209] (abstract) 2016 USA	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[210] (abstract) 2014 USA	56	-	-	Prevalent HD	Identify patient factors associated with dialysis adherence and IDWG	-	Veterans	None stated	STOFHLA	IDWG, dialysis knowledge	-
	Singh[211] (abstract) 2012 USA	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[213] (abstract) 2012 USA	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.	-

	Study Year Country	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)	Weng [184] 2013 USA	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)	-
	Wright [189] 2011 USA	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	-
	Wright-Nunes 1 [214] 2011 USA	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 [215] 2015 USA	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	-

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.[176, 197, 203] For two studies describing 341 patients,[197, 203] 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 are summarised in Table 3-2. Two studies used more than one health literacy measure.

Two studies included recruits to established clinical trials;[200, 212] 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[190, 199, 200] and high for one study.[204]

In Table 3-5, 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 3-7 and Table 3-8 along with covariates from multivariate models. Figure 3-5 shows effect sizes for associations tested in prospective analyses from cohort studies.

Table 3-5: 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)	**Laboratory measures** (Associated with clinical outcomes, including attainment of standards for dialysis quality)	**Clinical outcomes**
Non-dialysis CKD	Self-reported understanding of test results	Attendance vs non-attendance at transplant assessment	BP	Lipids	Progression to ESRD
	Objective kidney disease knowledge		Tobacco use	eGFR	Dialysis initiation
	Perceived kidney disease knowledge		Waist-Hip ratio		Atherosclerotic event (MI, Stroke, PVD)
	Patient satisfaction with clinician communication		Body mass index		Hospitalisation rate
	Sodium knowledge		Dietary intake		Mortality
	Knowledge of restricted foods				
	Awareness of CKD				
Dialysis	Improvement in Dialysis/transplant knowledge after education	Infection episodes	BP	Haemoglobin	Time to transplant referral
	Disaster preparedness	Hospitalisations	Dialysis catheter use	Haematocrit	Time to transplant wait-listing
	Medication label understanding	ED attendances	IDWG	Transferrin Saturation	Mortality
	Decision-making capacity	Missed dialysis sessions		Calcium	Kidney transplantation
	Medicines management capacity	Attendance vs non-attendance at transplant assessment		Phosphate	
	Self-reported medication adherence			Intact Parathyroid Hormone	
	Dialysis knowledge			Albumin	
				Kt/V	
Transplant	Medication non-adherence (by survey measure)			Transplant function	
	Decision-making capacity				

Table 3-6: Health literacy measures used: Systematic review of health literacy and clinical outcomes in CKD

Health literacy measure	Number of studies using measure (%)	Form	Approximate time taken	Health literacy categorisation
Short Test of Functional Health Literacy 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 Literacy 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 health literacy 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[190])	<1 minute	3-8 (or 0-5): Lower 9-14 (or 6-12): Moderate/Higher (<10/15 or <6/12 indicates limited health literacy)
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)[144]	0-1: High likelihood marginal/inadequate 2-3: Possible marginal/inadequate 4-6: Adequate (Here, <4 deemed limited health literacy[177])

Table 3-7: 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.

		Patient attributes															Processes of care					Clinical parameters													Lab measures													Clinical outcomes		
		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 preparaedness	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													•																																				
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Trans-plant	Gordon																																		o															
	Kazley													•																																				
	Weng	o																																																

Table 3-8: 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 marker:significant association. Unfilled marker: non-significant association. 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																									
			Patient attributes			Processes of care				Clinical parameters							Lab measures				Clinical outcomes							
	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																														
			Demographics						SES				Comorbidity										Dialysis			Study		Support					
	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		▨		▨	▨	▨	▨		▨			▨			▨	▨	▨	▨	▨	▨	▨											
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Dialysis	Adeseun		▨		▨	▨	▨		▨	▨																							
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	Grubbs			▨	▨	▨	▨		▨					▨														▨					
Transplant	Gordon		▨		▨	▨			▨	▨		▨									▨												

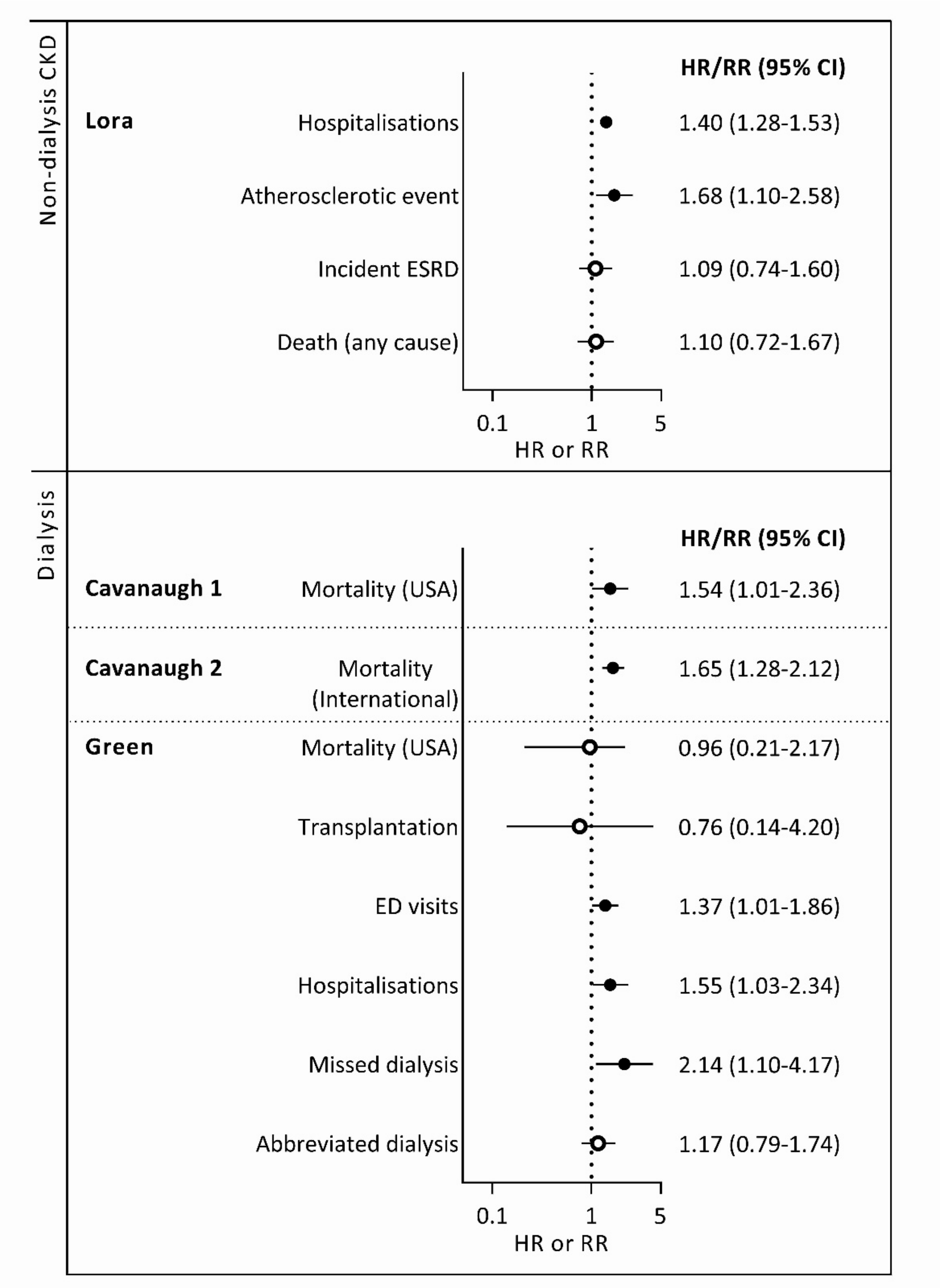


Figure 3-5: Summary of effect sizes for associations with limited (vs adequate) health literacy in cohort studies.

Covariates included in multivariate models are shown in Table 3-8. Cross-sectional results from baseline data in cohort studies not shown (shown Table 3-7 and Table 3-8) Results from Singla et al.[212] (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. HR: Hazard Ratio; RR: Rate Ratio; ED: Emergency Department;

The five cohort studies had a median sample size of 480 (IQR: 260-2392) and follow up times between 12 and 42 months (unknown for one study).[190]

Two studies reported on patients with non-dialysis CKD.[204, 212] 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. Another cohort study showed a significant univariate association between limited health literacy and hazard of dialysis initiation among 74 patients with CKD3-4.[212]

Three cohort studies reported on dialysis patients,[164, 190, 200] One 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.[200] Two cohort studies showed independent associations between limited health literacy and mortality in 480 incident haemodialysis patients from the USA[164] and 11,476 prevalent haemodialysis patients from multiple countries.[190] Both adjusted for demographics, but one did not adjust for comorbidity [190] and one did not adjust for SES.[164]

In results from cross-sectional studies, lower health literacy was independently associated with lower eGFR[177] and lower perceived[214] and objective[189] kidney disease knowledge among patients with non-dialysis CKD. Among dialysis patients, limited health literacy was independently associated with higher BP (diastolic and MAP)[173] and longer time to transplant referral[188] after adjustment for demographics and SES. An independent association between limited health literacy and dialysis catheter use was found in one study[199] without adjustment for SES. This finding conflicted with another study showing higher fistula use among those with limited health literacy by univariate analysis.[200]

3.4.3 Discussion

This novel systematic review explores associations between health literacy and clinical outcomes in CKD. Twenty-nine studies of 18,300 patients were identified, 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 in adjusted analyses to have significantly lower disease knowledge and understanding of test results, after adjustment for educational level.[189, 207, 214] 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. 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),[177] this finding was not supported by a high quality cohort study which examined the incidence of ESRD (Hazard Ratio, HR: 1.10; 95%CI: 0.74-1.60).[204]

Dialysis patients with limited health literacy were found to be at increased risk of mortality 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). These results may represent confounding by comorbidity and SES: one study failed to adjust for comorbidity,[190] while the other adjusted for comorbidity only as presence or absence of diabetes, and failed to adjust for SES.[164] A smaller cohort study which adjusted for both comorbidity and socioeconomic status[200] 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 (Table 3-8 and Figure 3-5). 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 observed higher blood pressure among dialysis patients with lower health literacy.[173] There was no consensus from several studies on a relationship between limited health literacy and haemodialysis access.[164, 199, 200, 206, 211] 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,[203] 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 therefore subject to survivorship bias.[188] Kidney transplant recipients, especially recipients of living-donor or pre-emptive transplants have significantly higher health literacy than dialysis patients[183, 207] and other surgical patients,[216] 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, wait-listing, living-donor transplantation, 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 [183, 217].

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:

- 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.
- 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.
- There was wide variation in the age, gender and ethnicity of participants, making comparison between studies difficult.
- Although additional information was obtained 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 [190, 204].

- 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[150, 152] 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.
- Although this review was registered with the international prospective register of systematic reviews, data collection had already begun at the time of registration.

In summary, this review demonstrates that a wide variety of outcome measures have been tested for association with health literacy in CKD. Nearly all available evidence is from the USA and is of low or moderate quality. The best quality evidence from cohort studies was for associations between limited health literacy and hospitalisations or cardiovascular events among patients with non-dialysis CKD, and with hospitalisation, missed dialysis and mortality among patients on dialysis. A need for evidence from outside the USA was identified, which is addressed in Chapter 6 of this thesis.

Chapter 4: The Access to Transplant and Transplant Outcome Measures (ATTOM) study: methods and introduction

4.1 Introduction

The Access to Transplant and Transplant Outcome Measures (ATTOM) programme is a UK research programme funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research. The programme undertook multiple work streams of quantitative and qualitative research. Methodology for the study is published in the study protocol.[218] This chapter outlines the methodology relevant to analyses presented in chapters 5 and 6.

4.2 Design, setting and participants

The ATTOM programme included a prospective, multicentre cohort study of patients with advanced kidney disease aged 18-75 years, from all 72 renal units operating in the UK at the time of patient enrolment (since which time two renal centres have merged and the total is now 71). Data from this study are used in the cross-sectional analyses in Chapter 5:, and the prospective analyses in Chapter 6:.

Patients were enrolled between December 2011 and September 2013 at three stages in treatment: within 90 days of starting dialysis (incident dialysis), while on the transplant waiting list (wait-listed) and within 90 days of transplantation (incident transplant). The process of patient enrolment and data collection is summarised in Figure 4-1. The wait-listed patients were selected as matched controls 1:1 to the incident transplant group based on age group, gender, time active on the transplant list and renal centre. Matching was performed to allow comparison of survival between these groups in a separate part of the ATTOM study not reported in this thesis.

Data were collected within 90 days of patient enrolment. Some patients transferred between groups during the study period, for instance wait-listed patients who were transplanted. In this situation, patients were recruited again and added as a separate patient record, contributing data to more than one group. Recipients of simultaneous pancreas and kidney transplants were included.

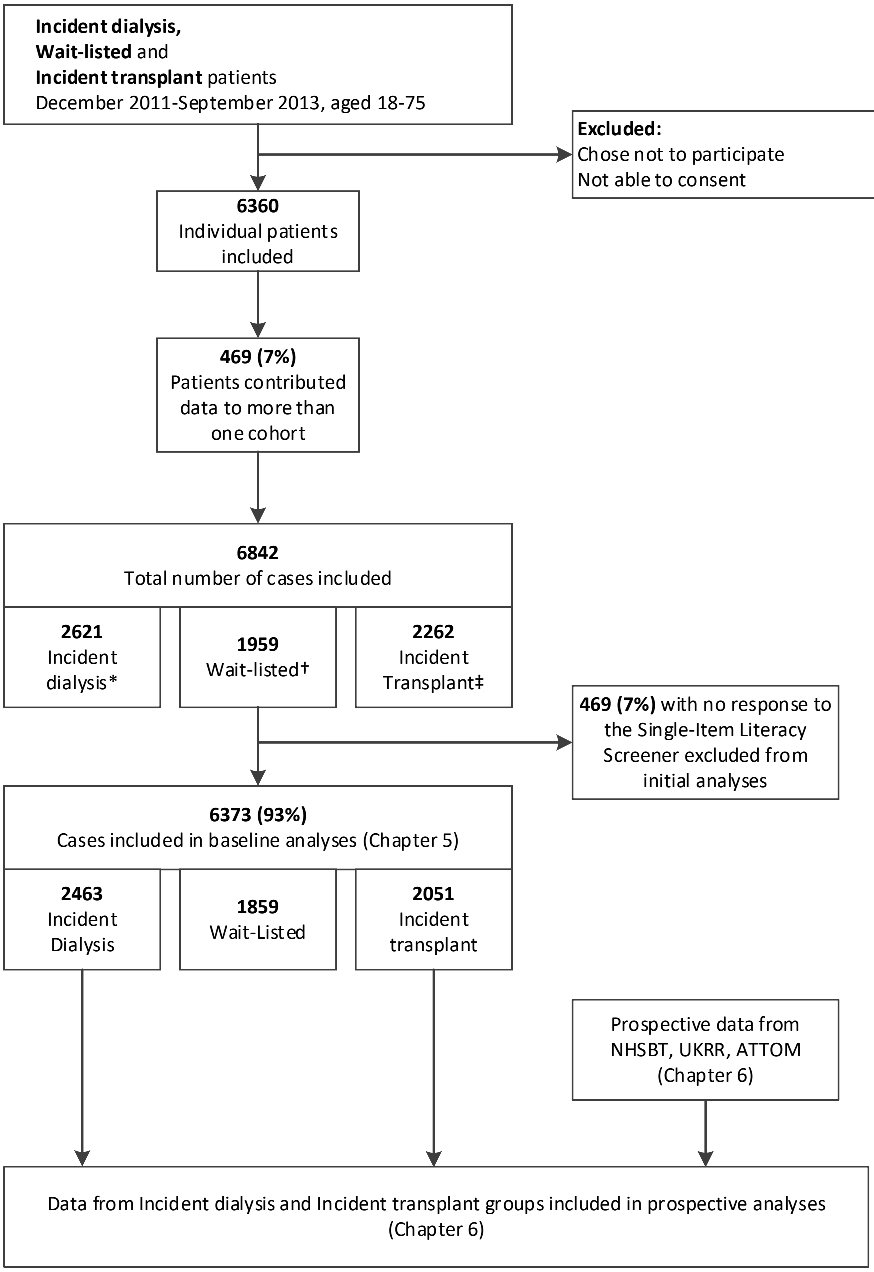


Figure 4-1: Enrolment of patients to ATTOM. Summary of data used for the analyses in Chapters 5 and 6.

* The proportion of patients recruited to the incident dialysis group is difficult to quantify because of differing start- and end-times of the research nursing contracts at each centre, although a comparison between patients recruited to ATTOM during 2012 and data from the UK Renal Registry showed that more than 50% of incident dialysis patients under 75 years were enrolled to ATTOM during that year.

† Includes 74% of patients transplanted in the UK during the study period. ‡ Includes 91% of wait-listed patients who were approached for inclusion.

Analysis of patients recruited to ATTOM versus non-recruited patients during 2012 showed that there were no significant differences in age, sex or ethnicity, after correction for missing ethnicity data in the UK Renal Registry database (data not shown)

4.3 Measures

Patients completed a questionnaire (Appendix C.1) which elicited demographic information, individual-level markers of socioeconomic status and responses to the SILS, a single-question measure of health literacy.[151] The questionnaire was self-completed except in cases of physical disability where help was given. Non-English interpretation was provided if required. For patients who were included in more than one group, case notes were reviewed again to record any change in comorbidities, but the patient questionnaire was not repeated.

Health literacy was measured using the Single-Item Literacy Screener (SILS): 'How often do you need to have someone help you when you read instructions, pamphlets or other written material from your doctor or pharmacy" Options were 1-Never, 2-Rarely, 3-Sometimes, 4-Often and 5-Always. A SILS score of >2 (ie: responses Sometimes, Often or Always) were selected to indicated limited health literacy. This decision was informed by validation work in which the SILS was compared to results from the Short Test of Functional Health Literacy in Adults (STOFHLA), a 36-item health literacy assessment tool. In one study of 999 adults with diabetes,[151] the SILS was found to be 54% sensitive and 83% specific for detecting limited health literacy as defined by STOFHLA score <23/36 (Table 2-1). A second study included 227 patients receiving haemodialysis,[156] reporting 39% sensitivity and 93% specificity for detecting limited health literacy. As such, the SILS lacks sensitivity to detect limited health literacy, and the implications of the use of SILS as a health literacy measure on the results are discussed in sections 5.5 and 6.6.

A proportion of patients did not return a response to the SILS and were excluded from initial analyses presented in Chapters 5 and 6. The implications of this missing data are discussed in these chapters. The results of multiple imputation of missing data are in Appendix D.2.

4.3.1 Modified Charlson comorbidity Index

Comorbidities were recorded from a structured review of case notes by a team of designated research nurses according to a pre-defined proforma. These comorbidities accounted for around 20 binary or free text data points per patient. In this thesis, comorbidity data is used to adjust for differences in comorbidity in order to demonstrate independent associations between health literacy and patient characteristics or outcomes. However, individual comorbidities were not included as covariates in multivariate models because this would have resulted in loss of statistical power, both by increasing the number of variables in the models, and requiring omission of records with missing data for a single comorbidity. Therefore, comorbidity data was combined into a single measure: a modified Charlson comorbidity index.

This index was developed from Hemmelgarn et al[219] 2003, who adapted the original Charlson index[220] to more accurately predict outcomes in patients in End-Stage Renal Disease. Some changes were made to allow for the data available from the ATTOM study. The index weightings, compared to those from Hemmelgarn's modified Charlson index are shown in Table 4-1.

Table 4-1: Score weightings for modified Charlson index based on Hemmelgarn et al

Comorbidity variables from Hemmelgarn et al	Weight	Corresponding variable from ATTOM	Weight
Myocardial infarction	2	Myocardial infarction	2
Congestive heart failure	2	Heart failure	2
Peripheral vascular disease (includes Aortic aneurysm >6cm)	1	Peripheral vascular disease or aortic aneurysm repair	1
Cerebrovascular disease	2	Cerebrovascular disease	2
Dementia	1	Dementia	1
Chronic lung disease	1	Respiratory disease	1
Rheumatological /Connective tissue disease	1	Excluded	-
Peptic ulcer disease	1	Excluded	-
Diabetes without complications	2	Diabetes, excluding those with diabetes as primary renal disease	2
Diabetes with complications	1	Diabetes as primary renal disease	1
Leukaemia	2	Leukaemia	2
Lymphoma (includes myeloma)	5	Lymphoma or myeloma	5
Moderate/severe liver disease	2	Liver cirrhosis	2
Metastatic cancer	10	Metastatic cancer	10
TOTAL SCORE	33		31

Presence of rheumatological or peptic ulcer disease were not recorded in the ATTOM study, so were excluded from the scoring. Score weightings were unchanged from the Hemmelgarn modified Charlson index. Some definitions were altered to allow for subtle differences in the way comorbidities were recorded. The small number of patients (92; 1.3%) with missing data for one or more diagnoses included in the Charlson index were scored at 'zero' for that diagnosis, but their total score was still included in the initial analyses.

Chapter 5: Limited health literacy prevalence and associations: analysis of baseline data from the ATTOM study

5.1 Preface

This chapter reports novel research based on data from the Access to Transplant and Transplant Outcome Measures (ATTOM) study. It has been published as:

Taylor DM, Bradley JA, Bradley C, Draper H, Johnson R, Metcalfe M, Oniscu G, Robb M, Tomson C, Watson C, Ravanan R and Roderick P. Limited health literacy in advanced kidney disease. Kidney International 90(3): 685-695 2016

The published paper can be found in Appendix A.

Additional material for this chapter is in Appendix D.

All of the analyses reported in this chapter and associated appendices were performed by DT. Retha Steenkamp (Statistican, UK Renal Registry) gave advice about the handling of missing data and guidance when fitting multiple imputation models.

5.2 Aim and Methods

This chapter presents analysis of baseline data from the ATTOM study as described in Chapter 1:.

The aim of this analysis was to determine the prevalence of limited health literacy and its associations with demographics, comorbidity and socioeconomic status in patients at three different stages of treatment: at initiation of dialysis, while on the kidney transplant waiting list, and at the point of kidney transplantation, and to consider the potential implications for patients' progress toward transplantation.

5.3 Statistical analysis

The outcome of interest was limited health literacy, defined by the response to the SILS.[151, 156] The exposure variables of interest were demographics, comorbidities and individual-level markers of socioeconomic status. To quantify comorbidity, a modified Charlson index was used, based on an index validated in populations with End-stage Renal Disease.[219, 220] Details of the score are provided in section 4.3.1.

The null hypothesis was that limited health literacy is independent of demographics, comorbidity and socioeconomic status in patients within 90 days of dialysis initiation, while on the transplant waiting list, and within 90 days of transplantation. In descriptive statistics, continuous variables are described as median (interquartile range) and binary variables as frequency (percentage) unless otherwise specified. The prevalence of limited health literacy and associated factors were analysed within each group. Univariate analyses were performed, using Mann-Whitney U tests for continuous variables, χ^2 or Fisher's Exact tests for binary variables as appropriate.

To examine the associations between patient-specific factors and health literacy, logistic regression models were fitted for each group, with limited health literacy as the dependent variable. Age (as a continuous variable), gender and ethnicity were included as independent variables in all models. A backwards-stepwise approach was used to select other variables for inclusion in the final model from those hypothesised to be associated with health literacy. These covariates were defined a priori and removed from the model if they failed to reach statistical significance ($p<0.05$). During the model-building process, the effect of adding the English fluency term on the relationship between ethnicity and health literacy was examined in each group. Interaction terms for Ethnicity/English fluency and Ethnicity/Car ownership and modified Charlson score/Car ownership were added to each model but removed from final models as they failed to reach statistical significance.

A small proportion (5-9%) of patients who agreed to participate in the ATTOM programme did not complete all or part of the patient survey, and around 1% of patients had missing comorbidity data because of inability to access case notes. Initially, regression models included data from complete cases only, so 628 cases (9%) were excluded. Patients with missing data were found to be significantly more likely to have diabetes or non-white ethnicity. To investigate the effect of these missing data, multiple imputation was performed, using 'imputation by chained equations' to produce 20 imputed datasets per group. These were used to fit regression models by the same backwards-stepwise approach, using data from all cases. Full details of this analysis are in Appendix D.2.

To compare the prevalence of limited health literacy between patients at different stages of treatment with adjustment for demographics, comorbidities and socioeconomic status, wait-listed patients were subdivided into those wait-listed pre-emptively (before starting dialysis) and those already on dialysis at the time of wait-listing. Transplanted patients were subdivided by pre-emptive transplantation versus transplantation after dialysis start and living- versus deceased-donor status. The prevalence of limited health literacy in these subgroups was then compared by univariate analysis. Where significant differences in limited health literacy prevalence were found, further logistic regression models were fitted, with limited health literacy as the dependent variable and patient subgroup as an independent variable. Sequential adjustment for factors shown to be associated with limited health literacy in the individual group analyses was then performed. Cases with missing data were excluded from these models, and where a model compared the prevalence of limited health literacy between two groups, patients recruited to both groups were excluded from the model.

All hypothesis tests were two-tailed. A p-value of <0.05 was deemed statistically significant. All statistical analyses were performed using Stata 12.1 (StataCorp LP, College station, TX, USA).

5.4 Results

A total of 6842 patients were recruited: 2621 incident dialysis patients, 1959 wait-listed patients and 2262 incident transplant patients, including 469 patients who contributed data to more than one group. The process of patient inclusion is shown in Figure 5-1

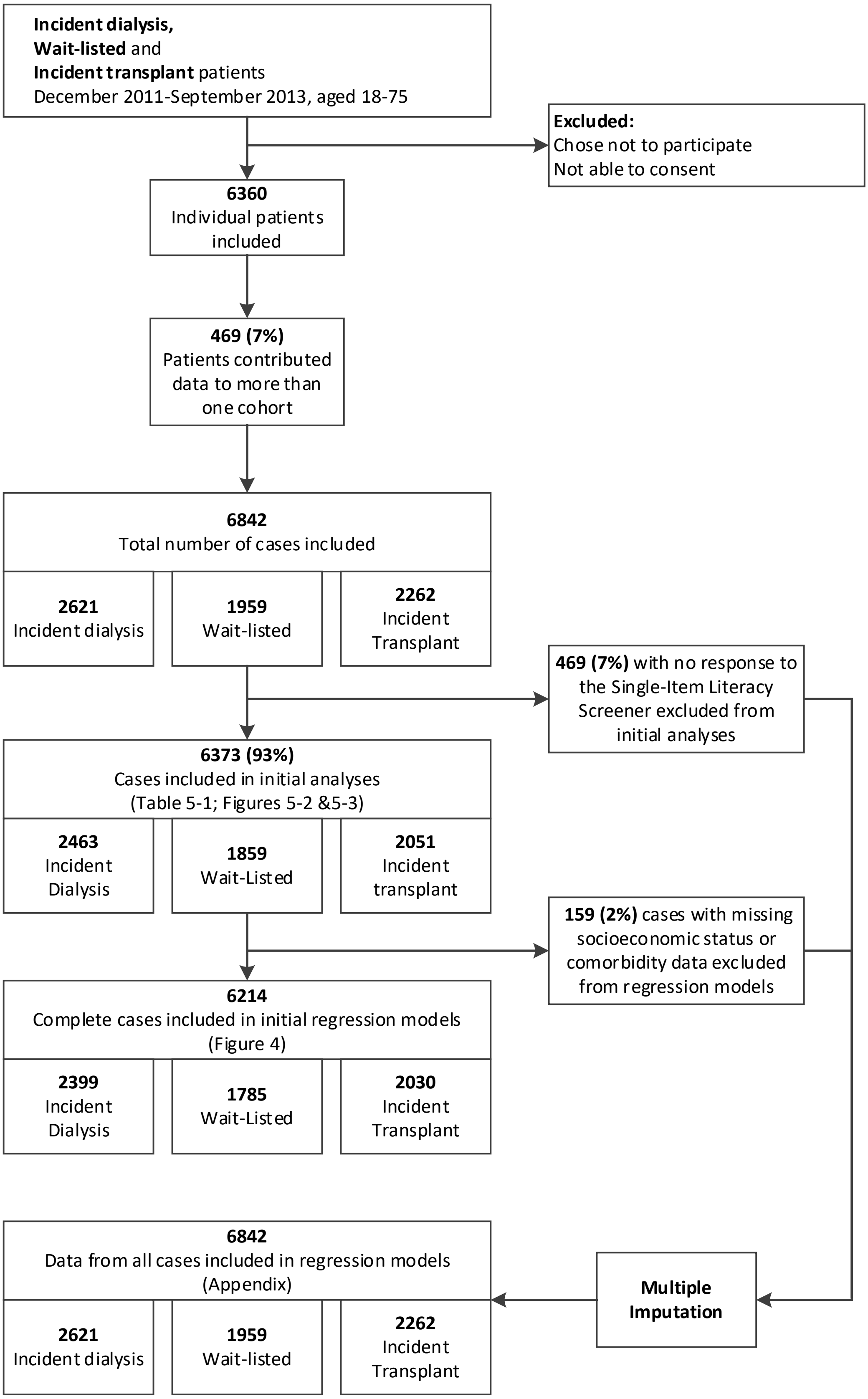


Figure 5-1: **Patient Inclusion process**

5.4.1 Prevalence of limited health literacy

Responses to the (SILS) in each group are shown in Figure 5-2. The prevalence of limited health literacy was 20% in the incident dialysis group, 15% in the wait-listed group and 12% in the incident transplant group. The distribution of individual SILS scores and the prevalence of limited health literacy differed significantly between groups (p<0.001). Figure 5-3 shows the patient pathways to transplantation and the prevalence of limited health literacy among patients in each group and subgroup.

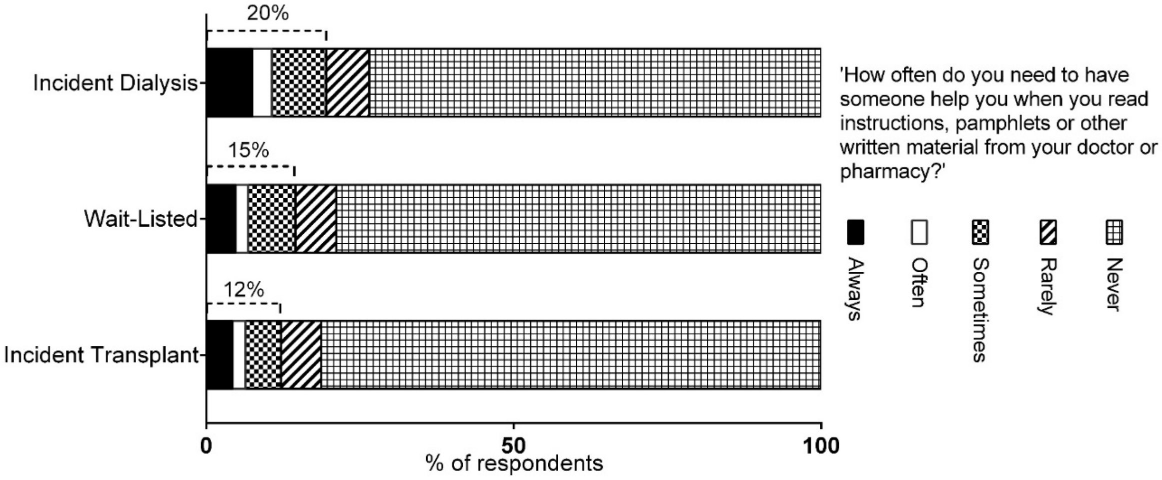


Figure 5-2: Responses to the Single-item literacy screener by patient group

Percentages indicate the prevalence of limited health literacy in each group. The distribution of responses was significantly different between groups by χ^2 test, p<0.001.

5.4.2 Associations with limited health literacy

Table 5-1 shows the patient characteristics and univariate analyses comparing patients with adequate and limited health literacy within each group. Figure 5-4 shows the results of fully adjusted logistic regression models identifying patient factors associated with limited health literacy.

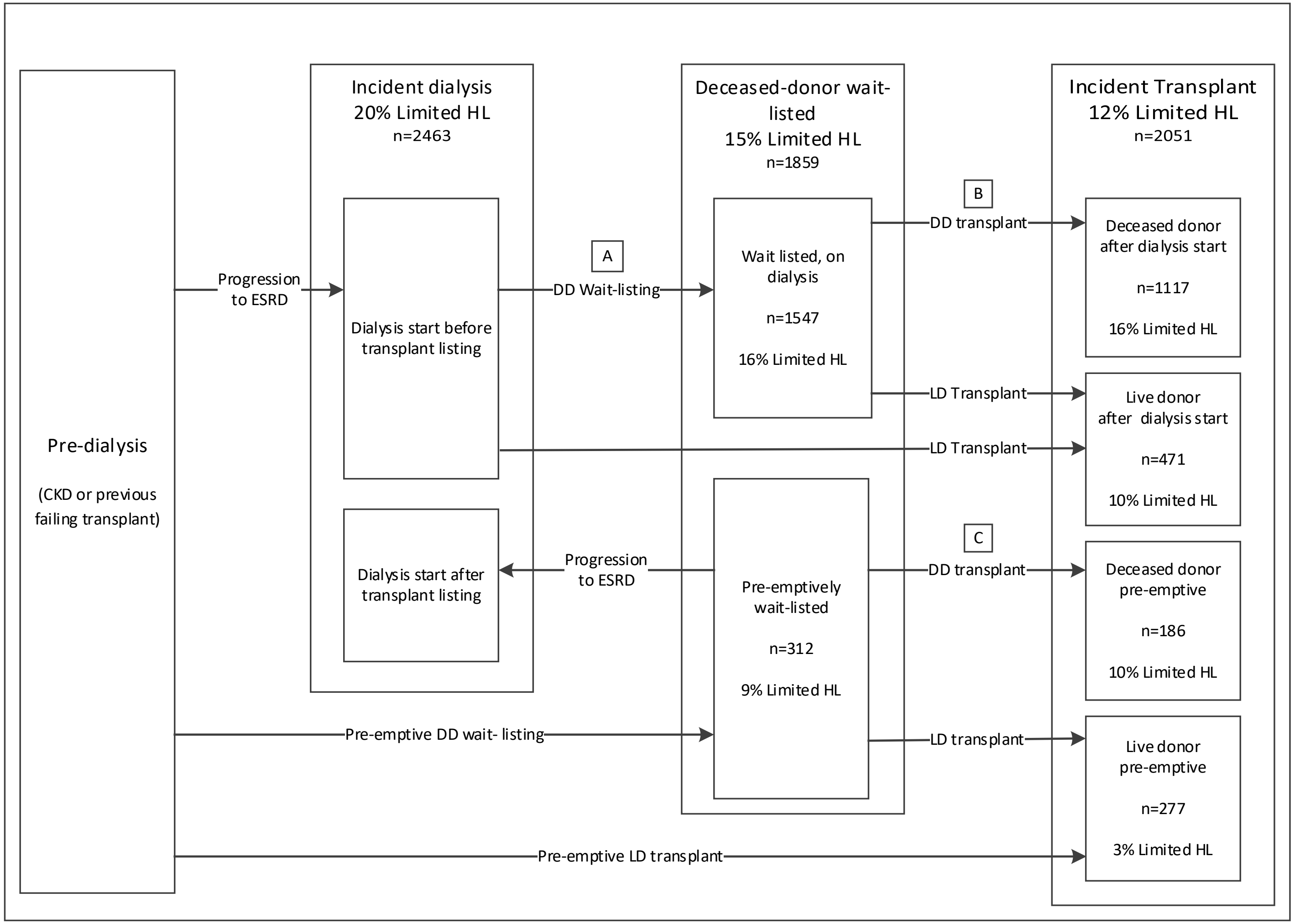


Figure 5-3: **Patient pathways to transplantation and the point prevalence of limited health literacy among patients at each stage**

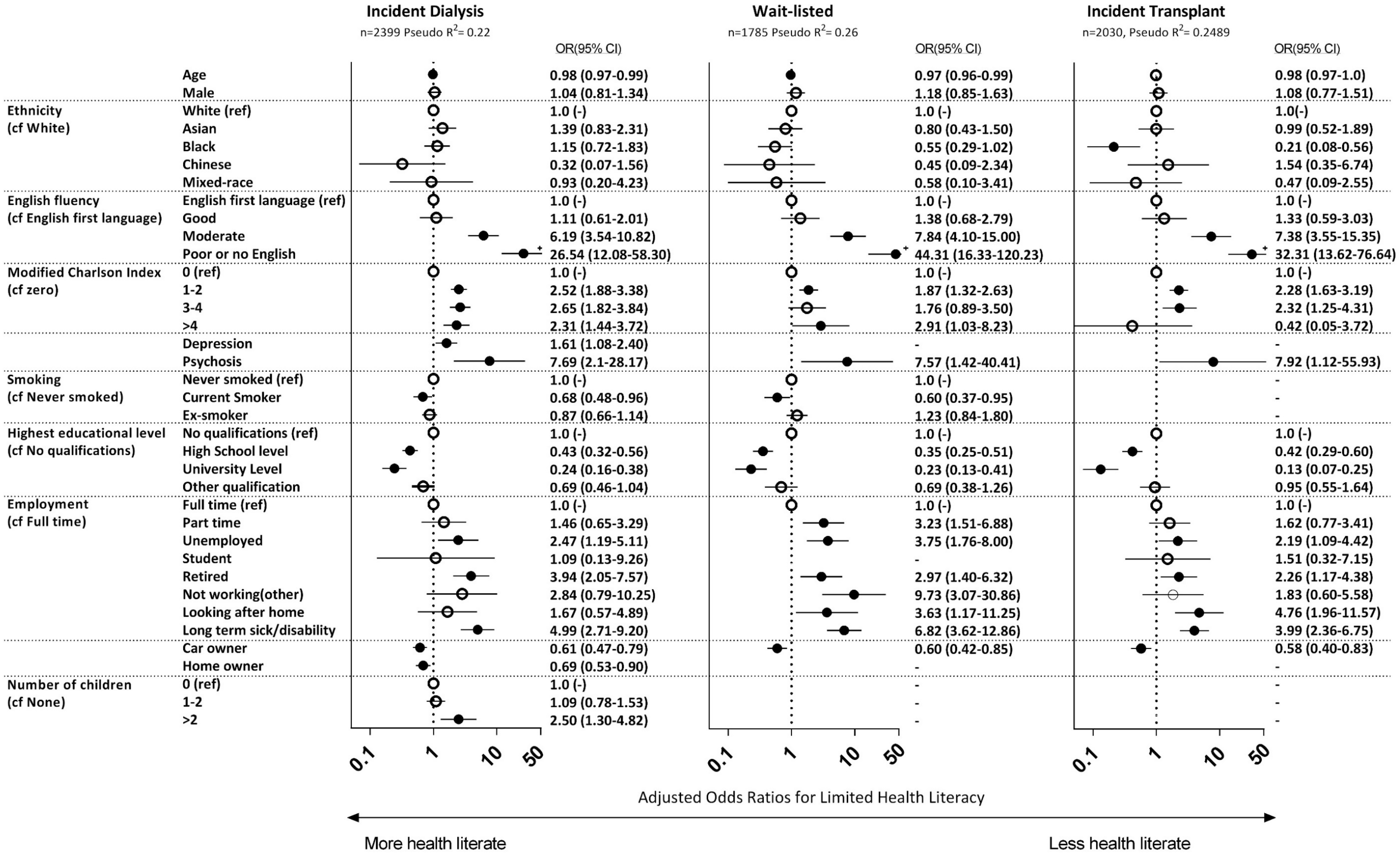
Markers A-C indicate points in patient pathways influenced by the deceased-donor transplant wait-listing and selection process. Most living donor recipients would have been added to the deceased-donor waiting list at the time of transplantation. LD: Living donor; DD: Deceased donor; ESRD: End-Stage Renal Disease; CKD: Chronic Kidney Disease

Table 5-1: Patient characteristics by group and health literacy status

Shown as frequency (percentage) unless otherwise specified. p-values indicate results of univariate analyses comparing those with adequate vs limited health literacy. Group percentages may not exactly equal 100% because of rounding.

	Incident dialysis, n=2463			Wait-listed, n=1859			Incident transplant, n=2051		
	Health Literacy			Health Literacy			Health Literacy		
	Adequate 1982 (80%)	Limited 481 (20%)	p	Adequate 1589 (85%)	Limited 270 (15%)	p	Adequate 1801 (88%)	Limited 250 (12%)	p
Male	1294 (65)	311 (65)	0.795	917 (58)	160 (59)	0.633	1128 (63)	152 (61)	0.575
Median age {IQR]	58 [47-67]	58 [47-66]	0.636	51 [41-61]	48 [39-58]	**0.008**	50 [39-60]	49.5 [41-58]	0.812
Ethnicity:									
White	1661 (84)	322 (67)	**<0.001**	1223 (77)	166 (61)	**<0.001**	1510 (84)	178 (71)	**<0.001**
Asian	140 (7)	107 (22)		153 (10)	68 (25)		137 (8)	52 (21)	
Black	140 (7)	39 (8)		173 (11)	26 (9)		118 (7)	8 (3)	
Chinese	15 (1)	6 (1)		20 (1)	7 (3)		11 (1)	8 (3)	
Mixed-race	25 (1)	7 (1)		19 (1)	3 (1)		24 (1)	4 (1)	
Language:									
English First Language	1800 (91)	338 (70)	**<0.001**	1390 (88)	168 (62)	**<0.001**	1647 (92)	167 (67)	**<0.001**
Other first language, self-reported English Fluency:									
Good	114 (6)	21 (4)		144 (9)	16 (6)		103 (6)	10 (4)	
Moderate	54 (3)	58 (12)		45 (3)	39 (14)		39 (2)	31 (12)	
Poor or no English	13 (1)	64 (13)		7 (0.4)	47 (17)		11 (1)	42 (17)	
Modified Charlson Comorbidity index:									
0	913 (46)	124 (26)	**<0.001**	1108 (70)	152 (56)	**<0.001**	1281 (71)	130 (52)	**<0.001**
1-2	692 (35)	230 (48)		400 (25)	95 (35)		422 (23)	99 (40)	
3-4	240 (12)	89 (19)		60 (4)	16 (6)		76 (4)	20 (8)	
>4	137 (7)	38 (8)		21 (1)	7 (3)		22 (1)	1 (0.4)	
Individual comorbidities									
Myocardial infarction	185 (9)	58 (12)	0.072	65 (4)	15 (6)	0.273	55 (3)	9 (4)	0.642
Heart failure	120 (6)	35 (7)	0.301	34 (2)	10 (4)	0.116	34 (2)	6 (2)	0.587
Peripheral vascular disease	159 (8)	58 (12)	**0.004**	55 (3)	12 (5)	0.413	50 (3)	15 (6)	**0.007**
Cerebrovascular disease	142 (7)	62(13)	**<0.001**	76 (5)	20 (8)	0.070	75 (4)	22 (9)	**0.001**
Dementia	4 (0.2)	0	1.0	3 (0.2)	0	1.0	1 (0.06)	0	1.0
Respiratory disease	214 (11)	59(13)	0.317	99 (6)	16 (6)	0.870	127 (7)	14 (6)	0.391
Diabetes	690 (35)	301(64)	**<0.001**	242 (15)	72 (27)	**<0.001**	293 (16)	88 (35)	**<0.001**
Diabetic nephropathy	417 (21)	216(46)	**<0.001**	156 (10)	59 (22)	**<0.001**	210 (12)	75 (30)	**<0.001**
Cirrhotic liver disease	23 (1)	4(1)	0.806	2 (0.1)	0 (0)	1.0	10 (1)	1 (0.4)	1.0
Leukaemia	5 (0.25)	1(0.2)	1.0	2 (0.1)	1 (0.4)	0.376	2 (0.1)	0	1.0
Lymphoma	20 (1)	2(0.4)	0.286	11 (0.7)	2 (0.7)	1.0	9 (0.5)	0	0.611
Psychosis	4 (0.2)	9(2)	**<0.001**	2 (0.1)	8 (3)	**<0.001**	2 (0.1)	5 (2)	**<0.001**
Depression	113 (6)	48(10)	**0.001**	89 (6)	18 (7)	0.5	74 (4)	15 (6)	0.118
Malignancy	263 (13)	41(9)	**0.006**	110 (7)	11 (4)	0.084	109 (6)	11 (4)	0.294

	Incident dialysis, n=2463			Wait-listed, n=1859			Incident transplant, n=2051		
	Health Literacy			Health Literacy			Health Literacy		
	Adequate 1982 (80%)	Limited 481 (20%)	p	Adequate 1589 (85%)	Limited 270 (15%)	p	Adequate 1801 (88%)	Limited 250 (12%)	p
Primary Renal Disease									
Diabetes	417 (21)	216 (45)	**<0.001**	156 (10)	59 (22)	**<0.001**	210 (12)	75 (30)	**<0.001**
Glomerulonephritis or SLE	389 (20)	63 (13)		450 (28)	42 (16)		522 (29)	46 (18)	
Polycystic Kidney Disease	185 (9)	23 (5)		272 (17)	36 (13)		286 (16)	25 (10)	
Pyelonephritis or TIN	144 (7)	23 (5)		179 (11)	32 (12)		204 (11)	19 (8)	
Hypertensive, renovascular or ischaemic nephropathy	188 (9)	35 (7)		104 (7)	17 (6)		113 (6)	18 (7)	
Other	659 (33)	121 (25)		428 (27)	84 (31)		466 (26)	67 (27)	
Smoking:									
Never smoked	1103 (56)	282 (59)	0.481	1005 (63)	175 (65)	0.773	1187 (66)	164 (66)	0.670
Ex-smoker	567 (29)	126 (26)		238 (15)	36 (13)		482 (27)	64 (26)	
Current Smoker	310 (16)	73 (15)		345 (22)	59 (22)		131 (7)	22 (9)	
Median BMI [IQR]	27 [23-32]	27 [24-33]	**0.022**	26 [23-29]	26 [23-30]	0.210	26 [23-29]	25 [23-29]	0.606
Highest Educational level:									
None	568 (30)	245(51)	**<0.001**	331 (21)	125 (47)	**<0.001**	311 (17)	112 (45)	**<0.001**
High-school level	858 (43)	156(33)		805 (51)	95 (35)		925 (52)	96 (39)	
University level	355 (18)	39(8)		340 (22)	25 (9)		436 (24)	14 (6)	
Other	193 (10)	40(8)		104 (7)	23 (9)		122 (7)	26 (10)	
Car owner	1479 (75)	272(57)	**<0.001**	1268 (80)	174 (65)	**<0.001**	1543 (86)	178 (71)	**<0.001**
Home owner	1135 (58)	191(40)	**<0.001**	934 (59)	106 (39)	**<0.001**	1163 (65)	125 (50)	**<0.001**
Marital status									
Married	1101 (56)	244(51)	**0.001**	801 (51)	128 (48)	0.770	957 (53)	127 (51)	0.595
Living with partner	135 (7)	22(5)		131 (8)	20 (7)		162 (9)	17 (7)	
Divorced or separated	240 (12)	85(18)		226 (14)	38 (14)		190 (11)	32 (13)	
Widowed	108 (5)	39(8)		55 (3)	10 (4)		52 (3)	7 (3)	
Single	388 (20)	89(19)		369 (23)	72 (27)		435 (24)	65 (26)	
Employment									
Full time	293 (15)	15 (3)	**<0.001**	399 (25)	15 (6)	**<0.001**	509 (28)	22 (9)	**<0.001**
Part time	163 (8)	18 (4)		206 (13)	23 (9)		192 (11)	15 (6)	
Unemployed	145 (7)	35 (7)		125 (8)	36 (13)		140 (8)	27 (11)	
Long-term sickness/disability	542 (27)	228 (48)		395 (25)	140 (52)		455 (25)	121 (49)	
Student	19 (1)	1 (0.2)		28 (2)	0		38 (2)	2 (1)	
Retired	741 (38)	166 (35)		363 (23)	41 (15)		370 (21)	39 (16)	
Not working (other)	28 (1)	5 (1)		23 (1)	6 (2)		50 (3)	7 (3)	
Looking after home	44 (2)	12 (3)		43 (3)	8 (3)		43 (2)	15 (6)	
Number of children									
0	1575 (80)	360 (75)	**0.001**	1165 (74)	189 (71)	**0.016**	1319 (73)	188 (75)	0.153
1-2	345 (17)	91 (19)		370 (23)	60 (22)		407 (23)	47 (19)	
>2	53 (3)	29 (6)		50 (3)	18 (7)		71 (4)	15 (6)	



		Incident Dialysis n=2399 Pseudo R^2= 0.22 OR(95% CI)	Wait-listed n=1785 Pseudo R^2= 0.26 OR(95% CI)	Incident Transplant n=2030, Pseudo R^2= 0.2489 OR(95% CI)
	Age	0.98 (0.97-0.99)	0.97 (0.96-0.99)	0.98 (0.97-1.0)
	Male	1.04 (0.81-1.34)	1.18 (0.85-1.63)	1.08 (0.77-1.51)
Ethnicity (cf White)	White (ref)	1.0 (-)	1.0 (-)	1.0(-)
	Asian	1.39 (0.83-2.31)	0.80 (0.43-1.50)	0.99 (0.52-1.89)
	Black	1.15 (0.72-1.83)	0.55 (0.29-1.02)	0.21 (0.08-0.56)
	Chinese	0.32 (0.07-1.56)	0.45 (0.09-2.34)	1.54 (0.35-6.74)
	Mixed-race	0.93 (0.20-4.23)	0.58 (0.10-3.41)	0.47 (0.09-2.55)
English fluency (cf English first language)	English first language (ref)	1.0 (-)	1.0 (-)	1.0 (-)
	Good	1.11 (0.61-2.01)	1.38 (0.68-2.79)	1.33 (0.59-3.03)
	Moderate	6.19 (3.54-10.82)	7.84 (4.10-15.00)	7.38 (3.55-15.35)
	Poor or no English	26.54 (12.08-58.30)	44.31 (16.33-120.23)	32.31 (13.62-76.64)
Modified Charlson Index (cf zero)	0 (ref)	1.0 (-)	1.0 (-)	1.0 (-)
	1-2	2.52 (1.88-3.38)	1.87 (1.32-2.63)	2.28 (1.63-3.19)
	3-4	2.65 (1.82-3.84)	1.76 (0.89-3.50)	2.32 (1.25-4.31)
	>4	2.31 (1.44-3.72)	2.91 (1.03-8.23)	0.42 (0.05-3.72)
	Depression	1.61 (1.08-2.40)	-	-
	Psychosis	7.69 (2.1-28.17)	7.57 (1.42-40.41)	7.92 (1.12-55.93)
Smoking (cf Never smoked)	Never smoked (ref)	1.0 (-)	1.0 (-)	-
	Current Smoker	0.68 (0.48-0.96)	0.60 (0.37-0.95)	-
	Ex-smoker	0.87 (0.66-1.14)	1.23 (0.84-1.80)	-
Highest educational level (cf No qualifications)	No qualifications (ref)	1.0 (-)	1.0 (-)	1.0 (-)
	High School level	0.43 (0.32-0.56)	0.35 (0.25-0.51)	0.42 (0.29-0.60)
	University Level	0.24 (0.16-0.38)	0.23 (0.13-0.41)	0.13 (0.07-0.25)
	Other qualification	0.69 (0.46-1.04)	0.69 (0.38-1.26)	0.95 (0.55-1.64)
Employment (cf Full time)	Full time (ref)	1.0 (-)	1.0 (-)	1.0 (-)
	Part time	1.46 (0.65-3.29)	3.23 (1.51-6.88)	1.62 (0.77-3.41)
	Unemployed	2.47 (1.19-5.11)	3.75 (1.76-8.00)	2.19 (1.09-4.42)
	Student	1.09 (0.13-9.26)	-	1.51 (0.32-7.15)
	Retired	3.94 (2.05-7.57)	2.97 (1.40-6.32)	2.26 (1.17-4.38)
	Not working(other)	2.84 (0.79-10.25)	9.73 (3.07-30.86)	1.83 (0.60-5.58)
	Looking after home	1.67 (0.57-4.89)	3.63 (1.17-11.25)	4.76 (1.96-11.57)
	Long term sick/disability	4.99 (2.71-9.20)	6.82 (3.62-12.86)	3.99 (2.36-6.75)
	Car owner	0.61 (0.47-0.79)	0.60 (0.42-0.85)	0.58 (0.40-0.83)
	Home owner	0.69 (0.53-0.90)	-	-
Number of children (cf None)	0 (ref)	1.0 (-)	-	-
	1-2	1.09 (0.78-1.53)	-	-
	>2	2.50 (1.30-4.82)	-	-

Figure 5-4: Results of multivariate logistic regression models for the odds of limited health literacy by patient group

Markers shown for variables included in each model. Filled markers indicate statistical significance. “+” indicates upper bound of confidence interval is >50. Absent markers indicate variables which didn’t reach statistical significance, so were excluded from the model. There were no students with limited health literacy in the wait-listed group.

In the incident dialysis group, fully adjusted models showed that limited health literacy was significantly associated with younger age, poorer English fluency, higher comorbidity, depression, psychosis, lower educational level, unemployment or long term disability (when compared to full time employment), the absence of car or home ownership and having more than two children. Current smoking was associated with reduced odds of limited health literacy.

Similar associations were found in the wait-listed group, although stronger associations between limited health literacy and unemployment or long-term disability were detected. Depression, absence of home ownership and number of children were not significantly associated with limited health literacy in the wait-listed group.

The incident transplant group showed similar patterns of association, except that patients of black ethnicity were significantly less likely to have limited health literacy compared to those of white ethnicity. However this association relates to a small number of observations: only 8 black patients in this group had limited health literacy.

Patients of Asian ethnicity had a significantly higher odds of limited health literacy compared to white patients, but these differences were not significant after adjustment for English fluency (Appendix D.1). Although lower educational level was associated with limited health literacy in all three groups, education did not predict health literacy entirely: between 3 and 10% of patients with university-level qualifications had limited health literacy.

After multiple imputation to account for missing data, the prevalence of limited health literacy in each group remained the same. Pooled estimates of logistic regression models from 20 imputed datasets in each group showed no major differences compared to the models including complete cases only. Results from these models are shown in the Appendix.

5.4.3 Comparison of patient groups

Figure 5-3 shows the patient groups and subgroups and relative prevalence of limited health literacy. Table 5-2 and Table 5-3 show univariate and multivariate analyses comparing the prevalence of limited health literacy between patient subgroups. Incident dialysis patients had a significantly higher prevalence of limited health literacy compared to wait-listed patients on dialysis (Figure 5-3, point A). This difference was statistically significant until adjustment for socioeconomic status, and adding adjustment for comorbidity further reduces the effect of group on the likelihood of limited health literacy.

Table 5-2: Comparison of limited health literacy prevalence in patient groups, univariate analyses

A-C refer to points in patient pathways indicated in Figure 5-3. Groups with statistically significant differences by univariate analysis are included in multivariate analyses in Table 5-3. *Excludes patients recruited into more than one group.

		Unadjusted odds ratio for limited health literacy (95% CI)	p
A: Wait-listed on dialysis compared to incident dialysis *	Incident dialysis (ref) Wait-listed, on dialysis	1 0.77 (0.64-0.92)	0.003
B: Incident deceased-donor transplant compared to deceased-donor wait-listed *	Wait-listed, on dialysis (ref) Deceased-donor transplant after dialysis start	1 0.95 (0.75-1.20)	0.677
C: Pre-emptive deceased-donor transplant compared to pre-emptively wait-listed *	Pre-emptively wait-listed (ref) Pre-emptive deceased-donor transplant	1 1.18 (0.68-2.06)	0.561
Pre-emptive listing or transplant compared to listing or transplant after dialysis start	Wait-listed, on dialysis (ref) Pre-emptively wait-listed	1 0.51 (0.32-0.78)	0.001
	Deceased-donor transplant after dialysis start (ref) Pre-emptive deceased-donor transplant	1 0.62 (0.35-1.03)	0.057
	Living-donor transplant after dialysis start (ref) Pre-emptive living-donor transplant	1 0.30 (0.13-0.62)	0.001
Living-donor transplant compared to deceased-donor	Deceased-donor transplant after dialysis start (ref) Living-donor transplant after dialysis start	1 0.61 (0.43-0.87)	0.005
	Deceased-donor pre-emptive transplant (ref) Living-donor pre-emptive transplant	1 0.30 (0.12-0.71)	0.002

Table 5-3: Sequentially fitted logistic regression models reporting odds ratios for limited health literacy between patient groups

*Excluding patients recruited into both incident dialysis and wait-listed groups. SES adjustment includes employment, car and home ownership and education. Comorbidity adjustment includes modified Charlson index.

		Model				
		1	2a	2b	3	4
		Age, sex	As model 1 +ethnicity/language	As model 1 +SES	As model 1 + factors in models 2a and 2b	As model 3 + comorbidity/ smoking/psychosis
Wait-listed on dialysis compared to incident dialysis *	OR (95% CI)	0.74 (0.62-0.89)	0.71 (0.58-0.86)	0.84 (0.69-1.01)	0.79 (0.64-0.97)	0.92 (0.74-1.14)
n=3698	p	0.001	0.001	0.070	0.027	0.439
Pre-emptively wait-listed compared to wait-listed on dialysis	OR (95% CI)	0.50 (0.33-0.77)	0.48 (0.30-0.77)	0.81 (0.51-1.28)	0.75 (0.46-1.25)	0.79 (0.48-1.31)
n=1783	p	0.002	0.002	0.368	0.272	0.355
Pre-emptive living-donor transplant compared to living-donor transplant after dialysis start	OR (95% CI)	0.32 (0.15-0.67)	0.35 (0.16-0.77)	0.46 (0.21-1.00)	0.55 (0.24-1.23)	0.55 (0.25-1.27)
n=704	p	0.002	0.009	0.049	0.146	0.163
Living-donor transplant after dialysis start compared to deceased-donor transplant after dialysis start	β (95% CI)	0.57 (0.40-0.82)	0.55 (0.38-0.81)	0.72 (0.49-1.04)	0.69 (0.46-1.03)	0.78 (0.52-1.17)
n=1566	p	0.002	0.002	0.084	0.068	0.225
Living-donor pre-emptive transplant compared to deceased-donor transplant after dialysis start	OR (95% CI)	0.34 (0.15-0.78)	0.33 (0.14-0.82)	0.47 (1.88-1.15)	0.53 (0.20-1.42)	0.53 (0.20-1.45)
n=373	p	0.011	0.016	0.097	0.205	0.218

By univariate analysis, there were no significant differences in limited health literacy prevalence between patients wait-listed on dialysis and recipients who underwent deceased-donor transplantation, excluding patients transplanted pre-emptively (point B) or between patients wait-listed pre-emptively and those who received a deceased-donor pre-emptive transplant (point C).

Pre-emptive living-donor transplant recipients had a significantly lower prevalence of limited health literacy than living-donor recipients transplanted after starting dialysis. In multivariate models, adding adjustment for socioeconomic status had the largest effect on the magnitude of this difference. Living-donor transplant recipients had a significantly lower prevalence of limited health literacy than deceased-donor recipients until adjustment for socioeconomic status, in both pre-emptively transplanted patients and those transplanted after starting dialysis.

5.5 Discussion

This is the first UK-wide research to examine the prevalence and associations of limited health literacy among patients with kidney disease, and to compare prevalence between dialysis and transplanted groups in a single population. This large nationwide study of over 6800 patients aged under 75 from every renal unit in the UK showed that limited health literacy was common with a prevalence of limited health literacy of 20% among incident dialysis patients, 15% among transplant wait-listed patients and 12% among incident transplant patients. Limited health literacy was associated with lower employment, lower educational level, absence of car and home ownership, lower English fluency and higher comorbidity.

The prevalence of limited health literacy was lower among patients on the transplant waiting list compared to those starting dialysis, and lower among transplanted patients compared to those on the waiting list. The most health-literate groups were living-donor transplant recipients and patients listed or transplanted pre-emptively, and this health literacy difference appears to be related to higher socioeconomic status and lower comorbidity. When living-donor and pre-emptively transplanted patients are excluded, significant differences in health literacy remain between incident dialysis and wait-listed patients, until adjustment for socioeconomic status and comorbidity. These results are consistent with the finding from the systematic review in section 3.3 that transplanted patients have a significantly lower prevalence of limited health literacy compared to patients with earlier CKD or on dialysis.

Patients of Asian ethnicity were more likely to have limited health literacy before adjustment for English fluency. Transplanted patients of black ethnicity had significantly higher health literacy than transplanted patients of white ethnicity. This contrasts with data from the USA, where black ethnicity is strongly associated with limited health literacy, even in transplanted patients.[164, 186, 200] This intriguing finding based on a small number of observations is investigated prospectively in section 6.4.3.

This analysis confirms an association between limited health literacy, low socioeconomic status and increased comorbidity in patients with advanced kidney disease found in Chapter 3. The explanation for these associations is likely to be complex. The cumulative complexity model (Section 2.3) describes the competing factors which affect patients' success in managing chronic disease in terms of 'burden of disease' and 'patient capacity' to cope.[146] Capacity is influenced by several factors including health literacy, financial and social support and functional effects of illness such as mobility and cognition. Limited health literacy therefore affects a group of patients with both impaired capacity and higher burden of disease. This imbalance between capacity and disease burden is likely to impair patients' success in navigating healthcare services, and may impede access to kidney transplantation. Higher health literacy levels were detected in wait-listed patients compared with incident dialysis patients, in living-donor transplant recipients compared to deceased-donor transplant recipients, and in pre-emptively listed or transplanted patients compared with those listed or transplanted after starting dialysis. In part, these differences may be explained by the exclusion of comorbid patients on the basis of poor fitness for transplantation, who may have lower health literacy as a result of cognitive impairment or from shared risk factors. Socioeconomic status also appeared important in explaining the health literacy gap between transplanted patients and those on dialysis. Lower socioeconomic status[9] and limited health literacy[188] are known to be associated with reduced likelihood of transplant wait-listing, and limited health literacy may act as one mediating factor in the effect of low socioeconomic status on patient outcomes including access to the transplant waiting list and to living-donor transplantation. However, there is an established strong association between multimorbidity and low socioeconomic status[114] which could lead to residual confounding after adjustment for modified Charlson index, and augment the apparent association between socioeconomic status, health literacy and access to transplantation.

This work benefits from nationwide coverage and the use of a simple, validated health literacy measure to report on a large number of patients. Patients from all renal centres were approached nationwide, reducing the risk of selection bias. The sample was broadly representative of the population[218], though the number of peritoneal dialysis patients was under-represented in the incident dialysis group, which would be expected to result in an overestimate of the true prevalence of limited health literacy among incident dialysis patients. The granularity of socioeconomic status data allowed the identification of associations between specific markers of poor socioeconomic status and health literacy. There was adjustment for an extensive list of comorbidities.

There are some limitations:

- The results must be interpreted with reference to the limitations of the SILS. As a complex, multifaceted construct, no measure can capture all elements of individual health literacy, although comprehension-based measures do attempt to assess directly different health literacy elements, which cannot be addressed by a single question. For example, the SILS does not directly measure numeracy skills, which are independently associated with the prevalence of chronic diseases.[145] The SILS has been validated against other health literacy measures. In a primary care study of 999 adults with diabetes, the SILS was validated against STOFHLA (a 36-question health literacy evaluation tool). A threshold for limited health literacy of >2 (as in this study) detected limited health literacy with a sensitivity of 54% and specificity of 83%.[151] A study of 227 haemodialysis patients reported similar results: 39% sensitivity and 93% specificity.[156] The results are therefore limited by the sensitivity of the SILS. More sensitive health literacy measures such as REALM (Rapid Estimate of Adult Literacy in Medicine) or STOFHLA may have addressed this limitation, but maybe at the cost of longer surveys increasing the burden on patients, resulting in a reduced response rate. It is unlikely that a response rate of 93% would be feasible if REALM or STOFHLA had been used instead of SILS. The use of the SILS to define limited health literacy may over- or under-estimate its true prevalence, although comparisons between the three treatment groups are likely to remain valid. The Brief Health Literacy Screener (BHLS) has now been used successfully to measure health literacy in CKD populations, and includes three screening questions. This measure may have been a better choice than the SILS, but it had not been validated in CKD populations at the time of ATTOM study design.[152]
- Patients over 75 and those unable to give informed consent were excluded, so these results cannot necessarily be applied to elderly patients or those with significant cognitive impairment. These results show that a large proportion of patients without overt cognitive impairment remain in need of help to understand health-related information.

- Patients who were enrolled in more than one group were not reassessed for health literacy when re-enrolled, so any improvement in health literacy during patients' progression towards transplantation could not be assessed.

In summary, these analyses confirm the association between limited health literacy, low SES and higher comorbidity among CKD patients in the UK, and reduced prevalence of limited health literacy as patients move along the pathway to transplantation. Recipients of living-donor or pre-emptive transplants had the lowest prevalence of limited health literacy. These results raise the possibility of inequity in the process of wait-listing for deceased-donor transplantation and access to living-donor transplantation, whereby differences in socioeconomic status and associated limited health literacy appear to reduce access to transplantation. The role of health literacy in these relationships is not clear, and the cross-sectional nature of these analyses makes causative inference impossible. In Chapter 6:, prospective analyses aim to identify the effect of limited health literacy on markers of success with renal replacement therapy, survival, access to transplantation and transplant function.

Chapter 6: Limited health literacy and patient outcomes: analysis of prospective data from the ATTOM study

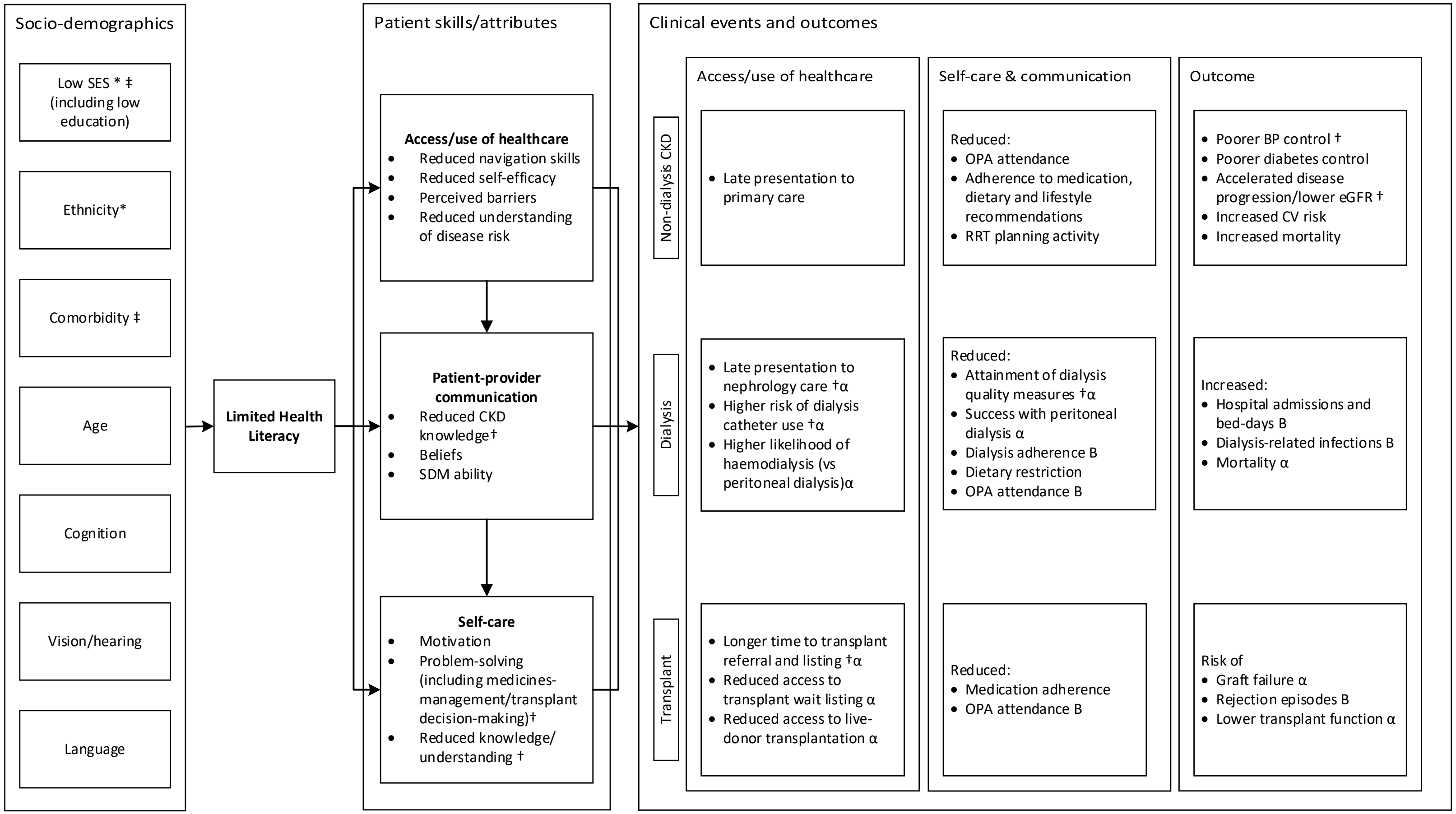
6.1 Preface

DT performed all of the analyses presented in this section and its associated appendix. Matthew Robb (Statistician, NHSBT) prepared the time-to-event variables to an agreed specification, in order to avoid the dissemination of identifiable data (dates of death etc.). The methodology for the mediation analysis in section 6.7 was developed by DT based on other published methods, and Ilya Shpitser (Statistician, Johns Hopkins University, Boston USA) provided specialist guidance on the validity of these methods. Additional material for this chapter are in Appendix E

6.2 Introduction

The prevalence of limited health literacy and its associations with demographic and socioeconomic factors are described in detail in Chapter 1: (by systematic review and meta-analysis) and in Chapter 5: (by novel investigation of patients from the UK ATTOM study). Limited health literacy was shown to be common among people with CKD, and to be associated with higher comorbidity and lower socioeconomic status (and in the USA, with non-white ethnicity). In section 3.4 a systematic review of the effects of limited health literacy on health outcomes in CKD identified some positive associations (all in US populations), but evidence in this area was limited, and many target areas for further research were identified. These included a need for prospective investigation into the effects of limited health literacy on dialysis quality, healthcare service use and access to transplantation, and for evidence from countries other than the USA.

Figure 6-1 shows a conceptual model of limited health literacy in CKD, adapted from Paasche-Orlow 2007[13] and Devraj 2009.[221] Socioeconomic and demographic associations identified in Chapters 3 and 5 are shown, along with hypothesised mechanisms by which limited health literacy may affect processes of care, and known and hypothesised associations with clinical outcomes in patients at different stages of treatment (non-dialysis, dialysis, transplant). In this chapter, data from the ATTOM study were used to investigate hypothesised associations between limited health literacy and several outcome measures. These outcome measures are described in Table 6-1, along with the sources of data. The postulated mechanisms by which limited health literacy could influence these outcomes are described below.



*** Findings from Systematic review of HL prevalence and associations**
† Findings from Systematic review of HL and outcomes
‡ Findings from ATTOM study HL prevalence and associations analysis
α Hypothesised associations for prospective investigation in Chapter 6
B Hypothesised associations for investigation using linked ATTOM/Hospital Episode Statistics data (not included in this thesis)

Figure 6-1: Conceptual model for the known and hypothesised effects of limited health literacy on outcomes in CKD

Adapted from Paasche-Orlow 2007[13] and Devraj 2009[221]. SDM: Shared decision-making; CV: Cardiovascular; ED: Emergency Department.

Table 6-1 Summary of outcome measures and their data sources. All analyses use ATTOM baseline data

ATTOM: Access to Transplant and Transplant Outcome Measures study; UKRR: UK Renal Registry; NHSBT: NHS Blood and Transplant. Hb: haemoglobin; CCa: Corrected Calcium; Phos: Phosphate; iPTH: intact Parathyroid Hormone; URR: Urea Reduction Ratio; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation.[24]

Outcome data	**Definition**	**ATTOM**	**UKRR**	**NHSBT**
Incident dialysis group				
Late presentation to nephrology	Dialysis start within 90 days of first contact with secondary care renal services	•		
Peritoneal dialysis as first dialysis modality	Peritoneal dialysis recorded as first dialysis modality	•		
Dialysis catheter as first haemodialysis access (compared to fistula/graft, Section 1.3.2.1)	For patients whose first dialysis modality was haemodialysis, dialysis catheter as first vascular access	•		
Peritoneal dialysis failure	Of patients alive and not transplanted at 12-15 months from peritoneal dialysis start, transfer to haemodialysis	•	•	
Laboratory variables (Hb, CCa, Phos, iPTH, URR, Section 1.3.2.3)	Laboratory values collected before dialysis in the 4th quarter after dialysis start (or 3rd quarter if 4th quarter data unavailable)		•	
Clinical dialysis parameters (dialysis modality, pre-dialysis SBP)	Clinical parameters collected before dialysis in the 4th quarter after dialysis start (or 3rd quarter if 4th quarter data unavailable)		•	
Time to deceased-donor transplant wait-listing	Time from dialysis start to deceased-donor transplant wait-listing, censored at loss to follow up or at 2 years (whichever earlier). Living-donor transplant recipients counted as listed 6 months before transplantation. Pre-emptively listed patients counted as time to listing of zero days.			•
Time to living donor transplantation	Time from dialysis start to living-donor transplantation, censored for deceased-donor transplantation, loss to follow up or at 2 years (whichever earlier)			•
Death on dialysis	Time from dialysis start to death, censored at loss to follow-up or at 2 years (whichever earlier)			•
Incident transplant group				
2 year creatinine and eGFR	Serum creatinine values collected at 2 years from transplantation. Calculated eGFR (CKD-EPI) using baseline age, sex and ethnicity data,	•		•
Time to transplant failure	Time from transplantation to transplant failure, censored for death with a functioning transplant, loss to follow-up or at 2 years (whichever earlier)			•

6.2.1 Hypothesised mechanisms for effect of health literacy on outcomes

Late presentation, dialysis modality, access and peritoneal dialysis failure

By reducing patients' understanding of CKD,[189] and use of preventative healthcare screening,[16] limited health literacy may result in reduced clinical contact with primary care, and therefore late referral to secondary care. The effectiveness of clinician-patient interactions in primary care is likely to be diminished. Once in contact with secondary care services, patients with impending ESRD are asked to be involved in decisions about dialysis modality and dialysis access. As described in section 1.3.2, home dialysis therapies (specifically peritoneal dialysis) are comparable in terms of dialysis efficacy, and have some benefits over hospital haemodialysis in terms of maintaining independence and preservation of residual renal function.[69, 70] However, patients who opt for peritoneal dialysis are required to manage their own dialysis treatment, which requires adequate understanding of the mechanism of the treatment, and problem solving skills. By contrast, hospital haemodialysis is in general a treatment delivered *to* the patient by dialysis staff, with less active participation by the patient.

By influencing patient understanding of the benefits of differing dialysis treatments, or confidence with self-care, limited health literacy may reduce the chance of patients opting for home dialysis therapies. Failure to adequately perform peritoneal dialysis treatment (for instance because of recurrent infection) may necessitate transfer to haemodialysis. In those who opt for haemodialysis as their initial dialysis modality, starting haemodialysis with a dialysis catheter for vascular access (as compared to a fistula or arteriovenous graft) is associated with poorer clinical outcomes,[66, 67] and guidelines therefore promote early formation of a fistula or graft.[68] Reduced health literacy may contribute to a reduction in patient capacity to effectively take part in dialysis planning and decision making, increasing the time needed to make decisions, and the likelihood of default to the quickest and often easiest method of establishing dialysis access: a haemodialysis catheter.

Dialysis: laboratory and clinical parameters

Assessment of the quality of dialysis delivery is undertaken by monitoring several laboratory and clinical parameters, including haemoglobin, phosphate and calcium and clinical parameters such as blood pressure and dialysis adequacy (by Urea Reduction Ratio, section 1.3.2.3). Although these parameters are likely to be influenced by patient comorbidity and the quality of service delivery by clinicians, patient factors may also have a role. For instance, serum phosphate is dependent on diet and adherence to phosphate binding medications (patient-controlled) as well as dialysis and medication dosing and dietician support (healthcare team-controlled). Understanding of dietary factors may be impaired by limited health literacy. Further, haemodialysis adequacy depends in part on treatment time. Haemodialysis treatment time is controlled by clinicians (by dialysis prescription) but in practice, patients may fail to attend individual dialysis sessions, or sessions may be curtailed at the patient's request. A lack of understanding of the adverse consequences of under-dialysis may lead those with low health literacy to miss more dialysis sessions or request shorter dialysis sessions.

Survival on dialysis

Adherence to dialysis treatment has been shown to be reduced in those with limited health literacy,[200] which could lead to inadequate dialysis treatment and increased risk of death. Failure to adequately understand the importance of dietary and fluid restrictions may lead to fluid overload or high blood potassium. In these situations, the fluid and electrolyte shifts produced by a dialysis session will be increased. These factors have been implicated in increasing the risk of death on haemodialysis.[222] Survival on dialysis was therefore investigated.

Transplant wait-listing and transplantation

In Chapters 3 and 5, wait-listed and transplanted patients have been shown to have a significantly lower prevalence of limited health literacy than those on dialysis. One mechanism which may explain this difference is selection of patients with higher health literacy for transplantation. It is feasible that patients with higher health literacy would be more likely to understand the benefits of transplantation earlier and make enquiries with clinicians about the transplantation process. Patients with low health literacy skills may be less likely to make such enquiries because of a lack of knowledge, a lack of confidence when interacting with clinicans,[13] or may be so overburdened[146] by the process of planning for dialysis that planning for transplantation is not prioritised. Potential living donors (family members) may be less likely to appreciate the benefits of living-donor transplantation to their relative, so be less likely to come forward as potential donors.

Transplant function and transplant failure

After transplantation, kidney transplant function is dependent in part upon adherence to medications (immunosuppressant drugs, antihypertensives etc.). The intended function of follow-up clinic appointments is to monitor transplant function, detect any problems and adjust treatment to extend the longevity of a transplant. Patients with limited health literacy may fail to understand the importance of consistent medication adherence or clinical follow up. Data on adherence to medication or clinical follow-up were not available, but lack of adherence could result in poorer transplant function or an increased likelihood of transplant failure: both of these outcomes are tested in this analysis.

6.3 Methods

The aim of this analysis was to establish if limited health literacy was associated with the above clinical outcomes, independent of demographics and comorbidity.

6.3.1 Baseline data

Methodology for the ATTOM study and a description of the health literacy, demographic and morbidity data collected at baseline is in Chapter 1:. For this analysis, PRDs were categorised according to UK Renal Registry criteria.[223] Data on timing of presentation to renal services, initial dialysis modality and dialysis access were recorded at baseline.

The proportion of missing data for the outcome variables are shown in Appendix E.2.

6.3.2 Incident dialysis group: laboratory and clinical parameters

For patients who were alive and were receiving dialysis 15 months after dialysis initiation, laboratory results and clinical data were obtained from the UK Renal Registry and Scottish Renal Registry. Data from the 4th quarter after dialysis initiation (12-15 months) were extracted and used for these analyses. In cases where 4th quarter data were unavailable, 3rd quarter data (9-12 months) were used if available (this applied to between 3% and 9% of cases).

Laboratory tests performed before a dialysis session included Haemoglobin (Hb, g/L), Phosphate (Phos, mmol/L), Corrected Calcium (CCa, mmol/L) and intact Parathyroid Hormone (iPTH, pmol/L). Urea reduction ratio (URR) and pre-dialysis systolic blood pressure (SBP, mmHg) were recorded for patients receiving haemodialysis (HD) or haemodiafiltration (HDF). These data were analysed as continuous variables, and used to establish if each patient met the relevant UK Renal Association clinical practice guideline standards applicable during the time of treatment.[224] These included Hb>10g/L, Phos<1.8mmol/L, CCa 2.2-2.6mmol/L, iPTH<9 x upper limit of normal (ULN) (<62pmol/L), URR>65% and SBP<160mmHg. iPTH results were not available from the Scottish Renal Registry, so data from Scotland were not included. Analysis of URR excluded patients receiving HD or HDF fewer than three times per week.

Dialysis modality data were used to identify patients whose initial dialysis modality was peritoneal dialysis, but who had transferred to haemodialysis at the time of data collection (‘peritoneal dialysis failure’). This analysis excluded patients who had died or received a kidney transplant at 15 months from dialysis start.

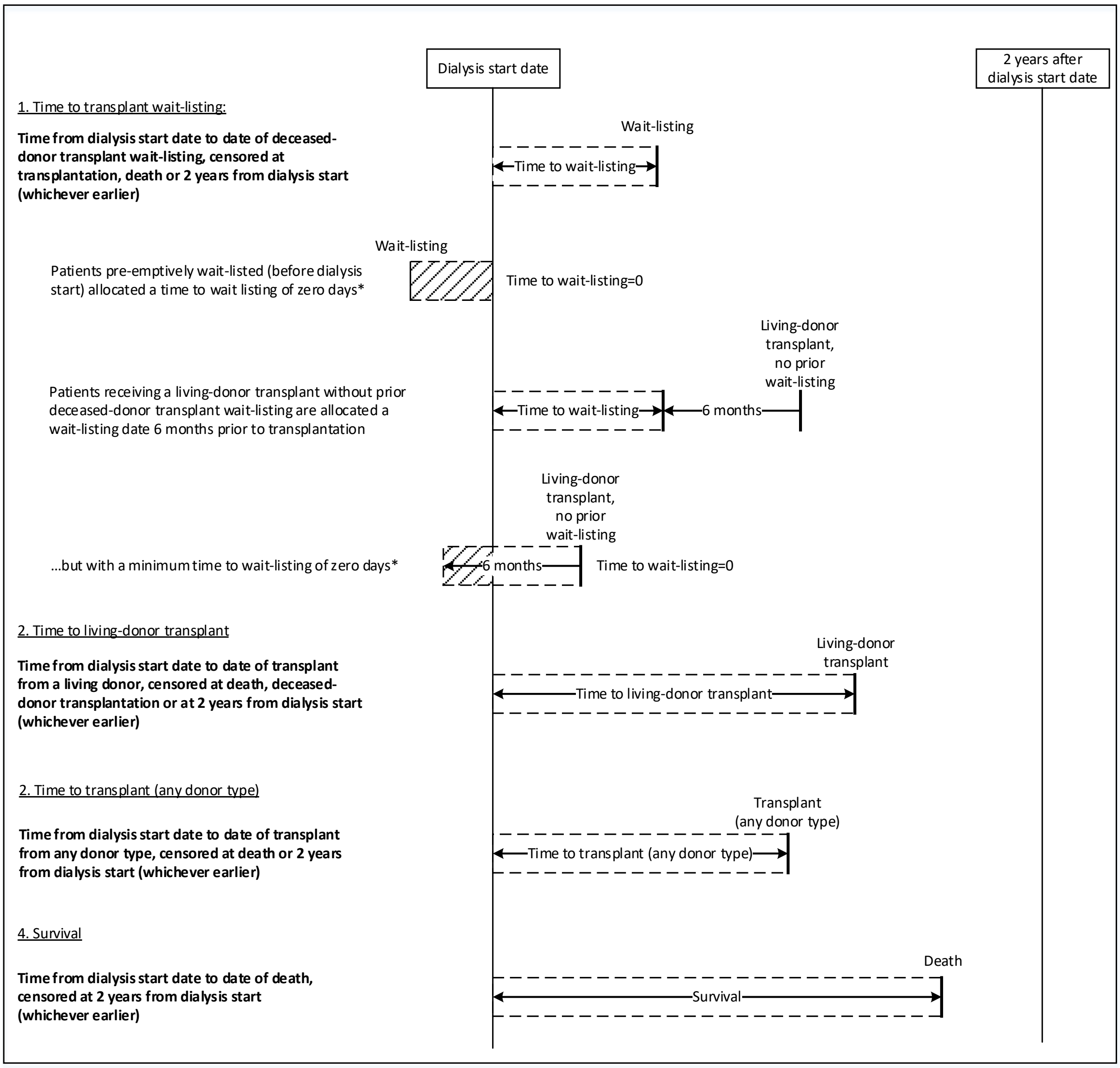
6.3.3 Incident dialysis group: time-to-event data

Incident dialysis patients were followed until September 2015. Data on transplant wait-listing, transplantation (including transplant type) and survival were collected via National Health Service Blood and Transplant (NHSBT).

These analyses excluded:

- Patients who recovered renal function and no longer required RRT (and hence had no indication for transplant; n=25)
- Patients previously recruited to the Incident Transplant group of the ATTOM study (n=24)
- Patients listed for multi-organ transplants (the prioritisation of which follows different protocols; n=8)

The specification of the individual time-to-event variables are given below, and described in



1. Time to transplant wait-listing:

Time from dialysis start date to date of deceased-donor transplant wait-listing, censored at transplantation, death or 2 years from dialysis start (whichever earlier)

Patients pre-emptively wait-listed (before dialysis start) allocated a time to wait listing of zero days*

Patients receiving a living-donor transplant without prior deceased-donor transplant wait-listing are allocated a wait-listing date 6 months prior to transplantation

…but with a minimum time to wait-listing of zero days*

2. Time to living-donor transplant

Time from dialysis start date to date of transplant from a living donor, censored at death, deceased-donor transplantation or at 2 years from dialysis start (whichever earlier)

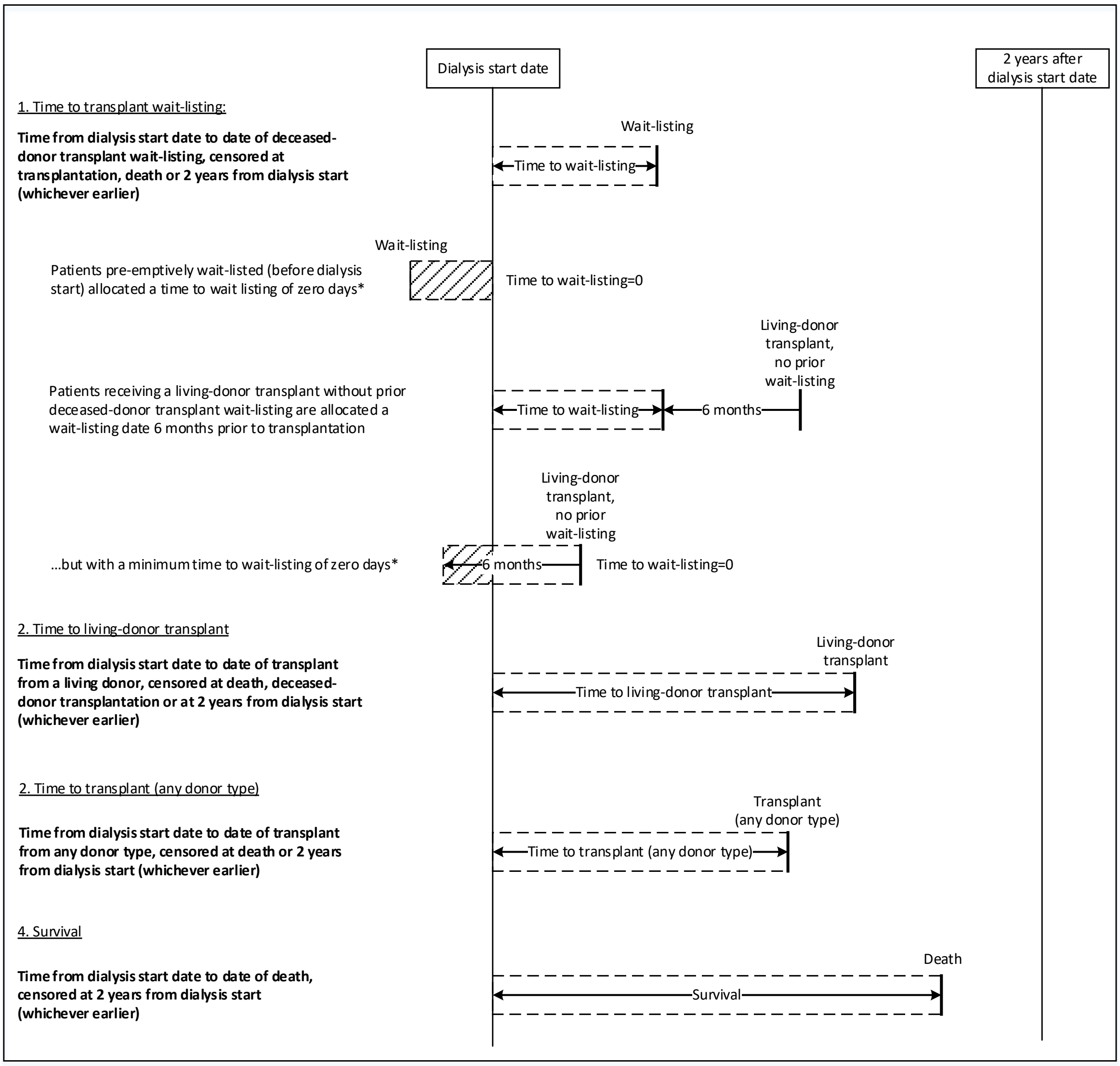
2. Time to transplant (any donor type)

Time from dialysis start date to date of transplant from any donor type, censored at death or 2 years from dialysis start (whichever earlier)

4. Survival

Time from dialysis start date to date of death, censored at 2 years from dialysis start (whichever earlier)

Figure 6-2.


1. Time to transplant wait-listing:

Time from dialysis start date to date of deceased-donor transplant wait-listing, censored at transplantation, death or 2 years from dialysis start (whichever earlier)

Patients pre-emptively wait-listed (before dialysis start) allocated a time to wait listing of zero days*

Patients receiving a living-donor transplant without prior deceased-donor transplant wait-listing are allocated a wait-listing date 6 months prior to transplantation

…but with a minimum time to wait-listing of zero days*

2. Time to living-donor transplant

Time from dialysis start date to date of transplant from a living donor, censored at death, deceased-donor transplantation or at 2 years from dialysis start (whichever earlier)

2. Time to transplant (any donor type)

Time from dialysis start date to date of transplant from any donor type, censored at death or 2 years from dialysis start (whichever earlier)

4. Survival

Time from dialysis start date to date of death, censored at 2 years from dialysis start (whichever earlier)

Figure 6-2: Specification of time-to event data

*Patients with a time to wait-listing of zero days are counted as ‘pre-emptively wait-listed’ in this section, so are not included in the Cox regression models reported in section 6.4.3 These patients are handled differently in the mediation analysis in Section 6.7.2.1.

Time from dialysis start to transplant wait-listing.

- Data were censored at transplantation, death or 2 years from dialysis start, whichever was earlier.
- Patients who received a living-donor transplant, but had not been formally wait-listed prior to transplantation were recorded as wait-listed 6 months before transplantation. This adjustment was to account for renal centres who may not add patients to the deceased-donor transplant waiting list during preparation of a potential living donor. The

adjustment assumes that a potential recipient is fit for transplantation 6 months prior to living-donor transplant

- Patients wait-listed before dialysis start ('pre-emptively') were excluded from this analysis. This included patients who received a living-donor transplant within 6 months of dialysis start without prior transplant wait-listing (and hence were allocated a time to listing of zero days). Patients wait-listed before dialysis start and any patient with a time to wait-listing of zero according to the above criteria were included in a separate analysis of pre-emptive transplant wait-listing (as a binary outcome variable).
- Patients who were wait-listed but were suspended from the waiting list for more than 30 days in the first 90 days of listing were excluded from this analysis. This is to account for the practice in some centres of wait-listing before immediate suspension while investigations are performed to ensure fitness for transplantation.

Time from dialysis start to living-donor transplantation.

Data were censored for death, deceased-donor transplantation, loss to follow-up, or at 2 years from dialysis start, whichever was earlier.

Time from dialysis start to transplantation (any donor type)

- Data were censored for death or at 2 years, whichever was earlier. No patients were lost to follow-up.

Sensitivity analyses for transplantation variables

- Because of a theoretical difference in the potential mechanisms by which health literacy may affect pre-emptive wait-listing, time to wait-listing, time to transplantation and time to living-donor transplantation, a sensitivity analysis was performed where patients who had previously been transplanted (n=298) were excluded**.** Patients who have previously received a transplant have already acquired knowledge of the process of transplantation, so the effect of limited health literacy may not be as marked compared to patients who had never been transplanted. Further, transplant recipients within the ATTOM study have been shown to have a significantly lower prevalence of limited health literacy than incident dialysis patients.
- These analyses aim to detect differences in access to deceased- and living-donor transplantation by health literacy. The pathway to a deceased-donor transplant includes two stages: time to wait-listing and time from wait-listing to deceased-donor

transplantation. The latter stage is controlled by transplant allocation policy, so individual patient characteristics which are not included in allocation algorithms (such as health literacy) would not be expected to have an effect. To confirm this, analysis of time from transplant wait-listing to deceased-donor transplant was performed. Patients were included if wait-listed prior to two years after dialysis start, and followed for two years from wait-listing, until death or until removal from the transplant list, whichever was earlier.

- In Chapter 5 (Section 5.4.2 and Figure 5-4), transplanted patients of black ethnicity had a significantly lower prevalence of limited health literacy than white patients, a difference not seen in the dialysis or wait-listed groups. To investigate this finding further, analysis of time to wait-listing, living-donor transplant and any transplant was repeated for black patients only.

Patient survival on dialysis.

- Data were censored at transplantation, loss to follow up, or at 2 years from dialysis start, whichever was earlier.

6.3.4 Incident transplant group: transplant function and transplant failure

Serum creatinine values were provided by NHS Blood and Transplant at 3, 12 and 24 months from the date of kidney transplantation. These were used to derive eGFR by the CKD-EPI equation[24] using demographic data (age, ethnicity, sex) collected at baseline. Patients whose transplant had failed and had restarted dialysis at 3, 12, or 24 months after transplantation were recorded as having an eGFR of 0ml/min/1.73m^2. Patients who had died at 3, 12 or 24 months were excluded from each analysis. Change in eGFR from 3 to 24 months and from 12 to 24 months was calculated. Differences in absolute eGFR and change in eGFR over time were compared between patients with limited vs adequate health literacy.

Incident transplant patients were followed for 2 years from the date of transplantation, and data on date of transplant failure (defined as return to dialysis after transplantation) were collected via NHSBT. Transplant failure data were censored at 2 years from transplantation, at death with a functioning transplant or loss to follow-up, whichever was sooner.

6.3.5 Statistical analysis

Descriptive statistics were calculated and summarised as mean (95% confidence interval), median [interquartile range], or number (percentage) as appropriate. Univariate analyses were performed using t-test or Mann-Whitney U test for continuous variables, and χ^2 test or Fisher's exact test for binary variables. Kaplan-Meier analysis and univariate Cox regression was performed for time-to event series variables. The proportionality assumption of each Cox model was tested globally and for each independent variable using Schoenfeld residuals.

Where significant associations between limited health literacy and any outcome measure was found by univariate analysis, multivariate analyses were performed using logistic regression for binary outcomes, linear regression for (normally distributed) continuous outcomes and Cox regression for time-to-event outcomes. In multivariate models, sequential adjustment for age, sex, ethnicity, English fluency, PRD and comorbidity (by modified Charlson index) was performed. Covariates in these models were selected if they showed significant associations with limited health literacy in analysis of baseline data ($p<0.05$; reported in Chapter 5), with the addition of PRD.

Adjustment for socioeconomic status is not performed here. As shown in Figure 6-1, health literacy is hypothesised to mediate the effects of low SES on outcomes. Including SES as a covariate in these models therefore does not reflect the hypothesised relationship. Instead, this relationship is explored in mediation models in section 6.7.

A p-value of <0.05 was defined *a priori* to represent statistical significance. All analyses were performed using Stata 12 (StataCorp LP, College station, TX, USA).

6.3.6 Missing data

Patients with missing data were excluded from individual analyses. Sequentially adjusted multivariate analyses exclude patients with missing data for any variable included in the fully adjusted model (ie: the model with age and sex adjustment includes the same subjects as the model with age, sex, ethnicity and comorbidity adjustment).

Analysis of missing data was performed to investigate its potential effects on results (Appendix E.2) The proportion of missing data was calculated for each outcome variable. For time-to-event analyses with significant results in multivariate models, unadjusted analysis was repeated comparing subjects with complete vs incomplete cases. For some example outcome analyses, the baseline characteristics of cases with complete vs incomplete records were compared.

6.4 Results: Incident dialysis group

ATTOM recruited 2,621 incident dialysis patients, 2,463 of whom responded to the SILS, and are included in the following analyses (Figure 4-1). Table 6-2 summarises patient demographics, morbidity and SES data, along with clinical and laboratory variables and p-values for univariate analyses. The results of multivariate analyses with adjustment for demographics, comorbidity and PRD are shown in Table 6-3. Details on missing data are shown in E.2.

6.4.1 Presentation, dialysis modality, haemodialysis access and peritoneal dialysis failure

By univariate analysis, limited health literacy was associated with reduced chance of late presentation to renal services (within 90 days of dialysis start). This association was not significant after adjustment for comorbidity and PRD.

There was no significant difference in the rate of haemodialysis catheter use as first dialysis access between those with limited vs adequate health literacy. Patients with limited health literacy were less likely to use peritoneal dialysis as their first dialysis modality, but this association was not significant after adjustment for ethnicity and language. Among patients whose initial dialysis modality was peritoneal dialysis, those with limited health literacy were more likely to have transferred to haemodialysis at 12-15 months. A comparable number in each group had been transplanted at this point (8.6% of those with adequate health literacy; 9.7% of those with limited health literacy). This difference was not significant after adjustment for PRD and comorbidity.

Table 6-2: Summary statistics and univariate analysis for the incident dialysis cohort

Shown as frequency (%), mean (95% CI) or median [IQR]. Subgroup percentages may not total 100% because of rounding. Significant p values shown in bold.

Incident dialysis group: n=2,463	**Health Literacy**		
	Adequate 1,982 (80)	**Limited 481 (20)**	
Male	1,294 (65)	311 (65)	0.8
Age	58 [47, 67]	58 [47, 66]	0.6
Ethnicity:			
White	1,665 (84)	319 (67)	**<0.001**
Asian	152 (8)	111 (23)	
Black	135 (7)	39 (8)	
Chinese	12 (1)	5 (1)	
Mixed-race	12 (1)	4 (1)	
Language:			
English First Language	1,800 (91)	338 (70)	**<0.001**
Other first language, self-reported English Fluency:			
Good	114 (6)	21 (4)	
Moderate	54 (3)	58 (12)	
Poor or no English	13 (1)	64 (13)	
Modified Charlson Comorbidity index:			
0	913 (46)	124 (26)	**<0.001**
1-2	692 (35)	230 (48)	
3-4	240 (12)	89 (19)	
>4	137 (7)	38 (8)	
Primary Renal Disease			
Diabetes	417 (21)	216 (46)	**<0.001**
Glomerulonephritis	314 (16)	59 (13)	
Pyelonephritis	128 (7)	20 (4)	
Hypertension	128 (7)	24 (5)	
Polycystic Kidney Disease	178 (9)	21 (4)	
Renovascular Disease	65 (3)	11 (2)	
Other	444 (23)	53 (11)	
Uncertain	286 (15)	68 (14)	
Highest Educational Qualification			
None	568 (30)	245 (51)	**<0.001**
High-school level	858 (43)	156(33)	
University level	355 (18)	39(8)	
Other	193 (10)	40(8)	
Car owner	1,479 (75)	272 (57)	**<0.001**

Incident dialysis group: n=2,463	**Health Literacy**		
	Adequate	**Limited**	
	1,982 (80)	**481 (20)**	
Home owner	1,135 (58)	191 (40)	**<0.001**
Employment			
Employed	456 (23)	33 (7)	**<0.001**
Unemployed or long-term sick/disabled	687 (35)	263 (55)	
Retired	741 (38)	166 (35)	
Other	91 (5)	18 (4)	
Late presentation (<90 days; excluding those previously transplanted)	299 (17)	41 (10)	**0.001**
Dialysis catheter as first dialysis access (if haemodialysis was first modality)	839 (55)	223 (57)	0.4
Peritoneal Dialysis as initial dialysis modality	424 (21)	81 (17)	**0.028**
Peritoneal dialysis failure (12-15 months)	59 (18)	19 (29)	**0.044**
Laboratory variables (12-15 months after dialysis start)			
Hb (g/L)	113 (112, 113)	110 (109, 112)	**0.009**
Corrected Calcium (mmol/L)	2.35 (2.34, 2.36)	2.33 (2.31, 2.35)	0.06
Phosphate (mmol/L)	1.60 (1.57, 1.62)	1.61 (1.56, 1.67)	0.5
intact PTH (pmol/L) (excludes Scotland)	28 [14, 49]	27 [15, 48]	0.9
URR (%) (if on HD or HDF>_3x/week)	74 [69, 78]	73 [68, 79]	0.9
SBP (mmHg) (if on HD or HDF)	142 (140, 143)	145 (142, 148)	0.08
Renal Association quality indicators			
Hb >10g/L	1,290 (84)	293 (80)	0.07
Corrected Calcium 2.2-2.6 mmol/L	1,227 (78)	285 (76)	0.3
Phosphate <1.8mmol/L	1,091 (70)	250 (68)	0.3
Intact Parathyroid Hormone <9xULN	1,037 (82)	241 (83)	0.6
Urea Reduction Ratio >65% (HD or HDF >_3x/week only)	642 (87)	188 (82)	0.07
Pre-dialysis systolic blood pressure <160mmHg	723 (80)	161 (72)	**0.010**
Access to Transplantation			
Pre-emptively wait-listed	247 (13)	44 (10)	**0.030**
At 2 years from dialysis start:			
Wait-listed	530 (33)	101 (24)	**0.001**
Transplanted (any donor type)	346 (18)	45 (10)	**<0.001**
Received living-donor transplant	167 (9)	15 (3)	**<0.001**

Table 6-3: Sequentially adjusted multivariate models for outcomes significantly associated with limited health literacy in univariate analyses in Table 6-2 and Figure 6-3.

Measures of effect shown for limited vs adequate health literacy depend on type of regression (Logistic: Odds ratio; Linear: β coefficient; Cox: Hazard ratio). Adjustment for Ethnicity, Language, PRD and modified Charlson index uses categories shown in Table 6-2 . Significant p-values are shown in bold.

		Model			
		1 Unadjusted	2 + Age/Sex	3 +Ethnicity/Language	4 +PRD/Comorbidity
Late presentation	OR	0.52	0.52	0.54	0.69
(<90 days)	(95% CI)	(0.37,0.75)	(0.37,0.74)	(0.37,0.78)	(0.47,1.02)
n=1930	p	**<0.001**	**<0.001**	**0.001**	0.07
PD as first dialysis modality	OR	0.75	0.75	0.77	0.80
(vs HD)	(95% CI)	(0.58,0.98)	(0.58,0.98)	(0.58,1.02)	(0.59,1.07)
n=2403	p	**0.035**	**0.034**	0.07	0.1
PD failure at 12-15 months	OR	1.85	1.83	2.00	1.67
(in PD was first dialysis modality)	(95% CI)	(1.00,3.41)	(0.98,3.40)	(1.02,3.89)	(0.82,3.37)
n=361	p	**0.049**	0.057	**0.043**	0.2
Haemoglobin	β	-2.10	-2.04	-2.15	-1.69
(pre-dialysis)	(95% CI)	(-3.78,-0.41)	(-3.72,-0.35)	(-3.96,-0.34)	(-3.54,0.17)
n=1878	p	**0.015**	**0.018**	**0.020**	0.07
Systolic BP <160	OR	0.63	0.63	0.62	0.78
(pre-dialysis)	(95% CI)	(0.45,0.88)	(0.45,0.88)	(0.43,0.89)	(0.53,1.14)
n=1111	p	**0.007**	**0.007**	**0.010**	0.2
Pre-emptively wait-listed	OR	0.68	0.68	0.72	0.85
	(95% CI)	(0.48,0.96)	(0.48,0.96)	(0.50,1.04)	(0.58,1.24)
n=2286	p	**0.029**	**0.027**	0.08	0.4
Chance of transplant wait-listing	HR	0.68	0.68	0.60	0.65
	(95% CI)	(0.55,0.85)	(0.54,0.84)	(0.47,0.75)	(0.51,0.82)
n=2004	p	**0.001**	**<0.001**	**<0.001**	**<0.001**
Chance of transplantation (any donor type)	HR	0.51	0.52	0.52	0.59
	(95% CI)	(0.37,0.70)	(0.38,0.72)	(0.37,0.73)	(0.42,0.83)
n=2369	p	**<0.001**	**<0.001**	**<0.001**	**0.002**
Chance of living-donor transplantation	HR	0.35	0.36	0.32	0.39
	(95% CI)	(0.20,0.60)	(0.21,0.62)	(0.18,0.57)	(0.21,0.70)
n=2372	p	**<0.001**	**<0.001**	**<0.001**	**0.002**

6.4.2 Dialysis quality indicators

Patients with limited health literacy had significantly lower haemoglobin concentration compared to those with adequate health literacy, but this difference was not significant after comorbidity adjustment. There were no significant differences in other laboratory variables between those with limited vs adequate health literacy.

Patients with limited health literacy were significantly less likely to achieve the UK Renal Association target of SBP <160mmHg, but this difference was not significant after adjustment for comorbidity. There was no significant difference in systolic blood pressure when analysed as a continuous variable. There were no other differences between those with limited vs adequate health literacy in the likelihood of achieving UK Renal Association clinical practice guideline standards.

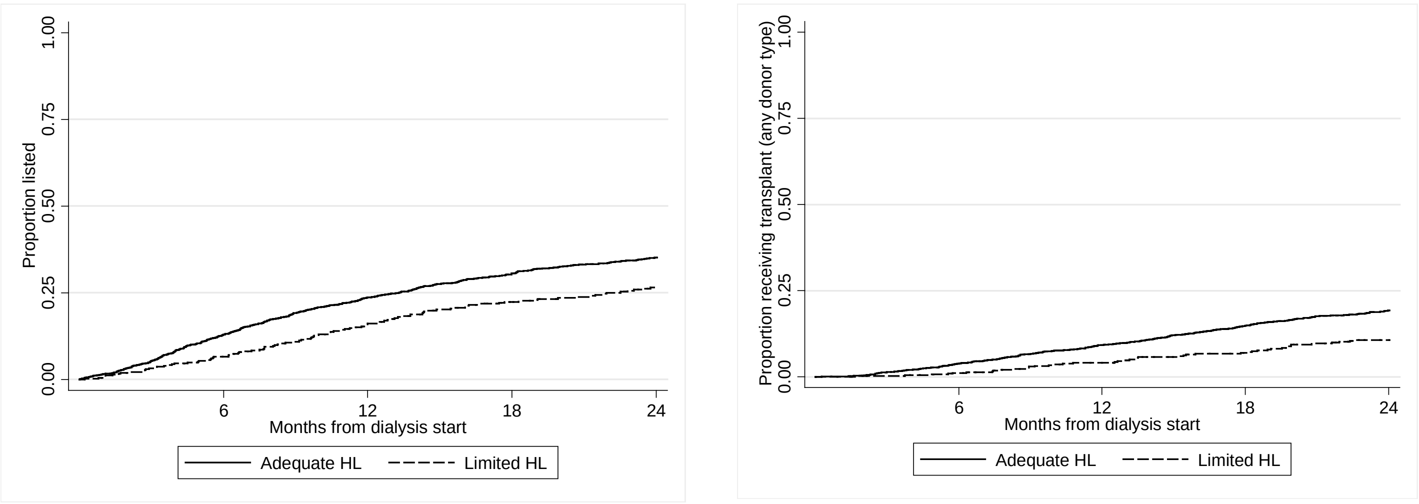
6.4.3 Transplant wait-listing, deceased- and living-donor transplantation, and survival on dialysis

In univariate analyses, patients with limited health literacy had a significantly lower chance of pre-emptive transplant wait-listing (Table 6-2), transplant wait-listing at 2 years, living-donor transplantation or transplantation from any donor type, but no difference in risk of death (Figure 6-3). At two years from dialysis start, compared to patients with adequate health literacy, a significantly lower proportion of patients with limited health literacy had been wait-listed (24% vs 31%), had received a living-donor transplant (3% vs 8%), or a transplant from any donor type (10% vs 24%) (Table 6-2). There was no difference between patients with limited vs adequate health literacy in the chance of deceased-donor transplantation after wait-listing (Appendix E.1.1)

In multivariate analyses, the association of limited health literacy with reduced transplant wait-listing, living-donor transplantation and transplantation from any donor type remained significant after adjustment for age, sex, ethnicity, language, comorbidity and PRD (Table 6-3).

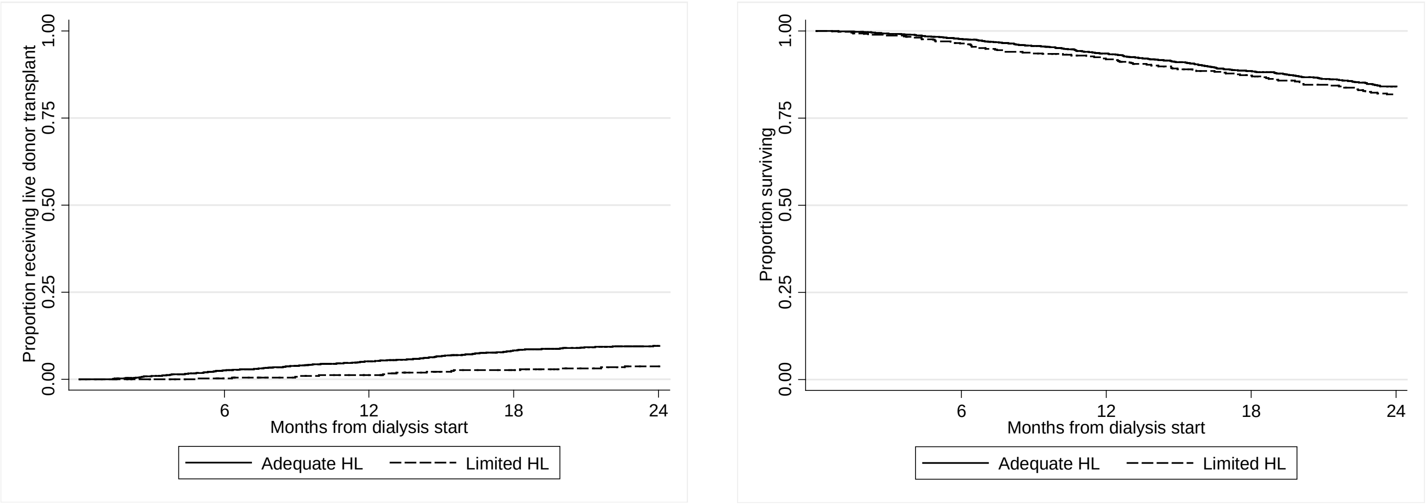
A sensitivity analysis which excluded previously transplanted patients in analysis of access to transplant wait-listing, transplantation (any donor type) and living-donor transplantation shows no difference in the pattern of results (Appendix E.1.2). Analyses restricted to black patients showed no significant difference in time to wait-listing between those with limited vs adequate health literacy (unadjusted HR: 0.60; 95% CI: 0.29-1.24), but this analysis included only 135 patients with 49 events. No black patients with limited health literacy (n=39) received a transplant within 2 years of dialysis start.

For the Cox regression models for time to transplant wait-listing and time to transplant (any donor type), the proportional hazards assumption was not violated. For the model of time to living-donor transplantation, the global test of the proportional hazards assumption showed no violation. On one level of the categorical exposure variable for English fluency, the test for violation of the assumption was significant, but re-fitting the model with stratification by this variable did not change the overall results (results not shown).



A: Time to transplant wait-listing, censored for death or transplantation

B: Time to transplant (any donor type), censored for death



B: Time to living-donor transplantation, censored for death and deceased-donor transplantation

D: Patient survival, censored for loss to follow up

Figure 6-3: Incident Dialysis group. Univariate analysis of time-to event variables, by limited vs adequate health literacy.

HR: Hazard ratio, HL: Health Literacy

	HR **(95% CI)**	**p**
A: Transplant wait-listing n=2034	0.69 (0.56, 0.86)	**0.001**
B: Transplantation (any donor type) n=2408	0.52 (0.38, 0.71)	**<0.001**
C: Living-donor transplantation n=2411	0.36 (0.21, 0.60)	**<0.001**
D: Death n=2419	1.16 (0.91, 1.49)	0.2

6.5 Results: Incident Transplant group

Of 2,051 incident transplant patients who were recruited, 1,801 responded to the SILS and are included in the following analyses (Figure 4-1) Summary data on demographics, language, comorbidity, SES and PRD are shown in Table 6-4.

There was no difference in transplant eGFR at 3, 12 or 24 months between patients with limited vs adequate health literacy. Further, there was no difference in eGFR change from 3-24 or from 12-24 months (Table 6-4). The proportional hazards assumption for time to graft failure was not violated. Univariate survival analysis showed no significant difference in the likelihood of transplant failure between those with limited vs adequate health literacy (Hazard ratio 1.6; 95% CI: 0.9-2.9; p 0.1).

Table 6-4: Summary statistics and univariate analysis for the incident transplant cohort

Shown as frequency (%) or median [IQR]. Percentages may not total 100% because of rounding.

Incident Transplant, n=2051	**Health Literacy**		
	Adequate 1801 (88%)	**Limited 250 (12%)**	**p**
Male	1128 (63)	152 (61)	0.6
Age	50 [39, 60]	49.5 [41, 58]	0.8
Ethnicity:			
White	1523 (85)	179 (72)	**<0.001**
Asian	135 (8)	53 (21)	
Black	116 (6)	8 (3)	
Chinese	10 (1)	5 (2)	
Mixed-race	14 (1)	3 (1)	
Language:			
English First Language	1647 (92)	167 (67)	**<0.001**
Other first language, self-reported English Fluency:			
Good	103 (6)	10 (4)	
Moderate	39 (2)	31 (12)	
Poor or no English	11 (1)	42 (17)	
Modified Charlson Comorbidity index:			
0	1281 (71)	130 (52)	**<0.001**
1-2	422 (23)	99 (40)	
3-4	76 (4)	20 (8)	
>4	22 (1)	1 (0.4)	
Primary Renal Disease			
Diabetes	210 (12)	75 (30)	**<0.001**

Glomerulonephritis	445 (25)	40 (16)	
Pyelonephritis	198 (11)	17 (7)	
Hypertension	92 (5)	15 (6)	
Polycystic Kidney Disease	284 (16)	22 (9)	
Renovascular Disease	26 (1)	3 (1)	
Other	366 (20)	47 (19)	
Uncertain	175 (10)	30 (12)	
Highest Educational Qualification			
None	311 (17)	112 (45)	**<0.001**
High-school level	925 (52)	96 (39)	
University level	436 (24)	14 (6)	
Other	122 (7)	26 (10)	
Car owner	1543 (86)	178 (71)	**<0.001**
Home owner	1163 (65)	125 (50)	**<0.001**
Employment			
Employed	701 (39)	37 (15)	**<0.001**
Unemployed or long-term sick/disabled	595 (33)	148 (60)	
Retired	370 (21)	39 (16)	
Other	131 (7)	34 (10)	
eGFR (CKD-EPI)			
3 months post-transplant	50.6 [37.4, 64.2]	51.9 [35.3, 66.7]	0.7
12 months post-transplant	52.5 [39.2, 66.3]	52.5 [39.0, 67.6]	0.8
24 months post-transplant	53.1 [39.2, 67.1]	51.8 [39.7, 68.4]	0.8
Change in eGFR			
3 to 24 months	0.98 (0.06, 1.90)	1.95 (-0.53, 4.43)	0.5
12 to 24 months	-0.16 (-0.85, 0.53)	1.02 (-0.61, 2.64)	0.2

6.6 Discussion

In this prospective analysis of the effect of health literacy on outcomes in patients with advanced kidney disease, incident dialysis patients with limited health literacy were significantly less likely to be wait-listed for transplantation, receive a living-donor transplant, or receive a kidney transplant from any donor type at two years from dialysis start, independent of demographics, PRD and comorbidity. Reduced chance of deceased-donor transplantation among those with limited health literacy appears to relate to differences in time to wait-listing (there was no significant difference in time from transplant wait-listing to deceased-donor transplant allocation). Several other outcome measures showed associations with limited health literacy until adjustment for demographics, PRD and comorbidity. These included earlier presentation to renal services, haemodialysis as first dialysis modality, peritoneal dialysis failure, lower haemoglobin, pre-emptive wait-listing and reduced chance of pre-dialysis systolic blood pressure <160mmHg. The remaining outcome measures, which included the majority of dialysis laboratory variables, survival on dialysis, transplant function and rate of transplant failure, were not significantly different in patients with limited vs adequate health literacy.

Health literacy appears to have independent effects on time to transplant wait-listing and time to transplantation from any donor, or specifically from a living donor, but not on other outcome measures. Arguably, outcome measures such as dialysis quality depend more on actions of the clinician: for the most part dialysis treatment is delivered *to* the patient. By contrast, the speed of the transplant preparation process depends on successful communication between patient and clinician to allow understanding of a complex procedure, and resulting planning and action *by* the patient. Low health literacy could impair this process by several mechanisms:

- Patients with limited health literacy may not adequately understand the benefits of transplantation over dialysis treatment, so may not prioritise the process of preparing for transplantation.
- Patients may be aware of their relative lack of health literacy, so may be intimidated by contact with clinicians,[139] and less likely to enquire about transplantation during clinical encounters.
- Discussion with family and friends may also be reduced as the importance of transplantation is not prioritised. Reduced social support (because of associated low SES) could compound this issue.
- Preparations for living-donor kidney transplantation require the potential recipient to understand the benefits of the treatment, and successfully communicate these ideas to a potential donor. This activity is likely to be difficult for those with lower health literacy.

- Even patients who understand the advantages of transplantation may be over-burdened by the process of preparing for or initiating dialysis, while the accumulating symptoms of advanced CKD may reduce their capacity to take part in preparations for transplantation.[107]
- Clinicians may identify patients with lower health literacy and be less likely to encourage transplantation because of the challenge of communicating with such patients, or concerns about their ability to cope with the process of transplantation or transplant follow-up.
- A potential living donor requires health literacy skills in order to understand the concept of living-donor transplantation as communicated to them by the potential recipient, and by the clinicians at the transplanting centre. As potential living donors are usually relatives, they may be from a similar sociodemographic group, and hence have a similar level of health literacy (increasing the challenge of communication) and higher levels of comorbidity (reducing the chance of being suitable as a living kidney donor) (Chapter 4: Prevalence and associations).

Among incident dialysis patients, late presentation was less likely among those with limited health literacy, until adjustment for comorbidity. This suggests that patients with higher comorbidity (who are also more likely to have limited health literacy), are appropriately referred earlier. This process is likely to be influenced by QOF targets in primary care, for CKD and diabetes (Section 1.4). Patients with limited health literacy were less likely to have peritoneal dialysis as their first dialysis modality, but this difference was not present after ethnicity and language adjustment. This may reflect reduced uptake of peritoneal dialysis in patients of non-white ethnicity, and warrants further research. Higher rates of peritoneal dialysis failure, lower haemoglobin concentration on dialysis and reduced attainment of dialysis blood pressure targets were found in those with limited health literacy, but these associations all appear to reflect confounding by comorbidity.

Several outcome measures showed no association with limited health literacy, even in univariate analyses. These included:

- No significant difference in the rate of dialysis catheter use in those with limited vs adequate health literacy. This negative finding in a large study is a significant addition to the available evidence, and conflicts with findings reported in smaller studies from the US” (Chapter 4).
- The majority of dialysis laboratory variables showed no difference by health literacy status. Attainment of UK Renal Association dialysis quality measures has also been shown

to be unaffected by socioeconomic status.[225] This is likely to reflect the fact that dialysis delivery is predominantly clinician- controlled, so patient factors do not have a significant effect on dialysis quality. Other studies have found negative associations between health literacy and dialysis quality measures (Chapter 4).

- Survival on dialysis was not associated with health literacy status. This result is consistent with health literacy as a mediator of SES differences in the UK, where differences in survival on dialysis by SES are not significant in adjusted analyses[8] and are likely to be attributable to comorbidity. This finding conflicts with data from the USA[164] and international data,[190] where mortality is significantly increased among those with limited health literacy. This may reflect differences in healthcare systems: in the UK where healthcare is free at the point of use, patients with lower health literacy (who have higher comorbidity and lower socioeconomic status) may experience fewer impediments in access to treatment compared to equivalent patients in other countries. Further, the studies from the USA which associate low health literacy with mortality may be at risk of residual confounding by comorbidity and SES (Section3.3.3).[164, 190] Lastly, even the detailed comorbidity data included in the ATTOM study does not account for the severity of individual comorbidities or changes in comorbidity over time.
- Health literacy did not appear to influence kidney transplant function or the risk of transplant failure among incident transplant patients. Transplant function is influenced by multiple clinical factors, including immunological match, donor characteristics and surgical and medical factors unrelated to recipient comorbidity. Data on these factors were not available so could not be taken into account.

These analyses benefit from a large sample size representative of the UK incident dialysis population (Chapter 5), detailed data on comorbidity, and relatively complete data for time to wait-listing and transplantation variables. The ability to adjust for detailed demographic and comorbidity variables (with greater completeness compared to registry data) increases confidence in these results. There are some limitations:

- These results are limited by the reliability of the SILS in measuring health literacy (these issues have been discussed in detail in Chapter 5).
- The laboratory and clinical data provided by the UK Renal Registry are collected within a 4-month period, and in some cases, data from the previous quarter were used. As such, these data were not collected at a set time point from dialysis start in all patients, which could bias results.
- The time-to-event variables for transplant wait-listing, transplantation, mortality (incident dialysis group) and transplant failure (incident transplant group) were censored at 2 years.

As such, event-rates are relatively low. Ideally, longer follow-up times would be used. Analysis of black patients only had a low event rate and no events for transplantation were recorded during the follow-up period. The ATTOM study continues to collect prospective data on these patients such that future analyses could include longer follow-up times.

- As discussed above, although the available comorbidity data were detailed, these do not account for the severity of comorbidity or change in comorbidity over time. Patients with lower health literacy may have more severe individual comorbidities and may more quickly develop further comorbidities during follow-up. As such, residual confounding by comorbidity is a possibility. Future linkage to Hospital Episodes Statistics data will allow examination of prospective comorbidity data.
- Although these results demonstrate a relationship between health literacy and wait-listing, living- or deceased-donor transplantation, data were not available to examine the reasons for these relationships. Data on patients' knowledge and understanding of the transplantation process would help to investigate this further and may be a focus of future study.
- Several variables had significant amounts of missing data, and initial exploration showed significant differences between patients with incomplete vs complete records. However, for the main positive findings in this chapter: differences in access to transplantation by health literacy, the proportion of missing data for the outcome variable was very low. These analyses were affected by missing data for other variables included in multivariate models. Analysis of time to transplant wait-listing, living-donor transplant, or transplantation from any donor type between patients with complete vs incomplete records showed no significant differences (Appendix E.2.2). This finding is not consistent with a significant effect of missing data in these models. For other outcome variables, there were significant differences between cases with complete vs incomplete data (Appendix E.2.3). It may be helpful to use multiple imputation and perform complete case analysis. However, deciding which data to impute in this case could be problematic: laboratory variables were not collected at a set time after dialysis start (or transplantation). If, for instance, a patient died at the end of the fourth quarter after dialysis start and a value for haemoglobin was not returned during that quarter, it would not be possible to ascertain if the missing data relate to non-return of data (imputation appropriate) or death (ie: imputation inappropriate). Excluding patients who had died by the end of this period could result in bias in the imputed model. Further, the imputation performed as part of the analyses for Chapter 5 (in Appendix D.2) showed no major differences in the pattern of associations between limited health literacy and

demographics or comorbidity. For these reasons, I have chosen not to perform multiple imputation of these data.

By showing that patients with limited health literacy have reduced access to transplantation, even after adjustment for clinical and demographic factors, these results suggest inherent inequity in the process of preparing patients for transplantation. Work in this thesis shows the strong associations between limited health literacy and markers of low SES, while SES has established associations with reduced access to transplantation.[9, 10] Several studies suggest that health literacy may promote inequity by acting as a mediator in the association between low SES and health.[157, 158, 160] In the next section, the potential mediating effect of health literacy in the association between low SES and reduced access to transplantation is investigated.

6.7 Health literacy as a mediating factor in the relationship between socioeconomic status and access to transplantation

6.7.1 Introduction

The results reported above show that limited health literacy is associated with indicators of reduced access to transplantation (deceased- and living-donor), after adjustment for demographics, comorbidities and PRD. This adjustment aims to eliminate confounding by the patient characteristics used in clinical practice to select appropriate transplant recipients, which also have associations with health literacy. Figure 6-4 illustrates the relationship between health literacy, access to transplantation, and the patient factors adjusted for in the above analyses.

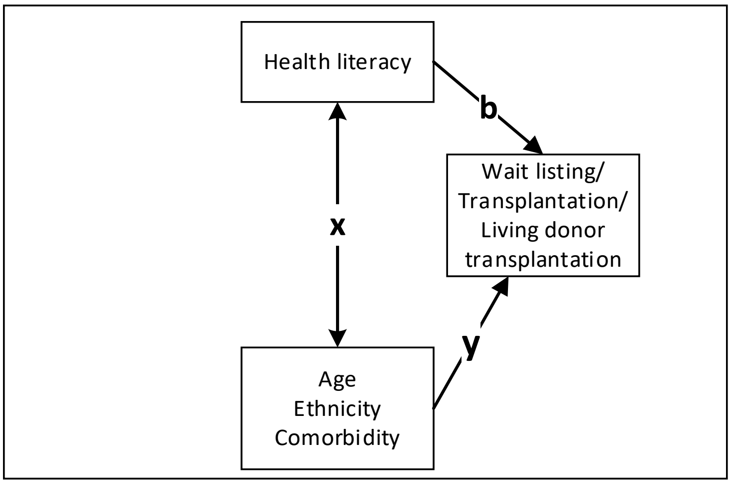


Figure 6-4: Conceptual model for the effect of health literacy on access to transplantation with adjustment for potential confounders as in section 6.4

After adjustment for these patient factors which are known to influence access to transplantation (Section 1.3.2.5) and also have associations with health literacy (Chapters 3 and 5), the resulting measured effect of limited health literacy on access to transplantation is equivalent to the true effect of health literacy, *and any other confounders* (pathway b). Other confounders which are not used in the clinical process of transplant allocation include SES. Significant associations between these factors and access to transplantation are likely to indicate *inequity* in transplant access.

If SES was hypothesised to confound the association between health literacy and access to transplantation by similar pathways to (for instance) comorbidity, then a measure of SES could be included in the above models as a covariate, in order to estimate the effect of health literacy on access to transplantation. However, this model would not match the hypothesised causal pathway in which health literacy acts as a mediating factor between SES and outcomes (Section 2.2.1.3). Instead, the exploratory analyses in this section are based on a mediation model, illustrated in Figure 6-5 and in the simplified version in Figure 6-6 (where pathways to potential confounders are not shown).

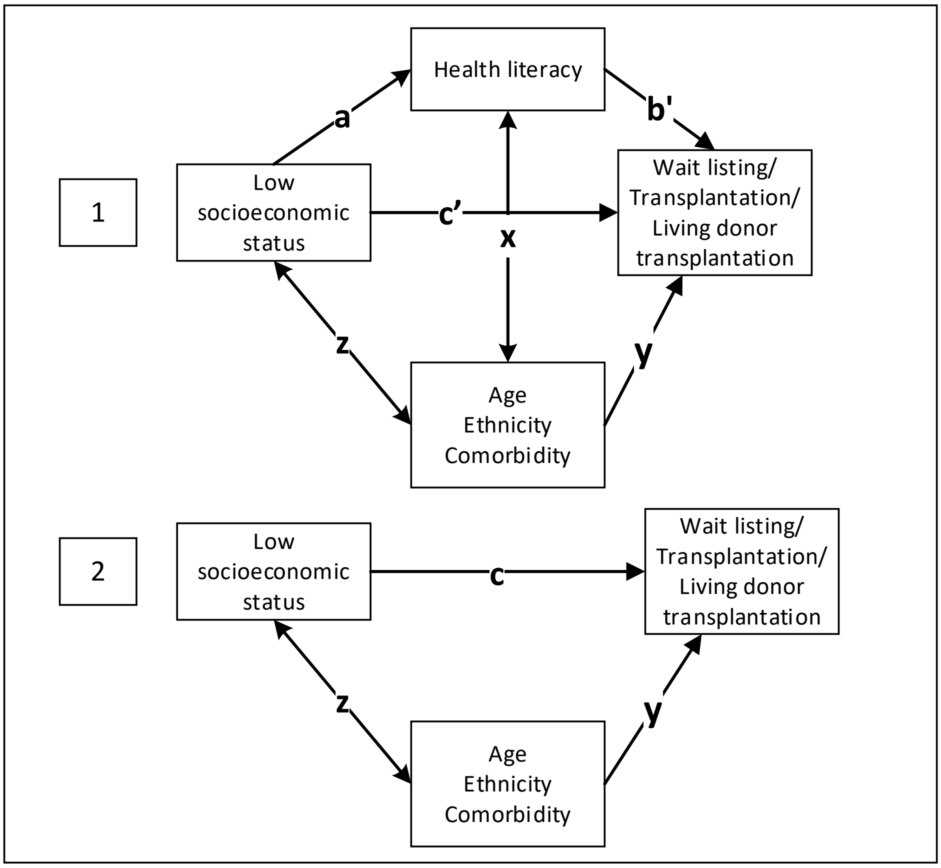


Figure 6-5: **Model for health literacy as a mediator in the association between low socioeconomic status and access to transplantation**

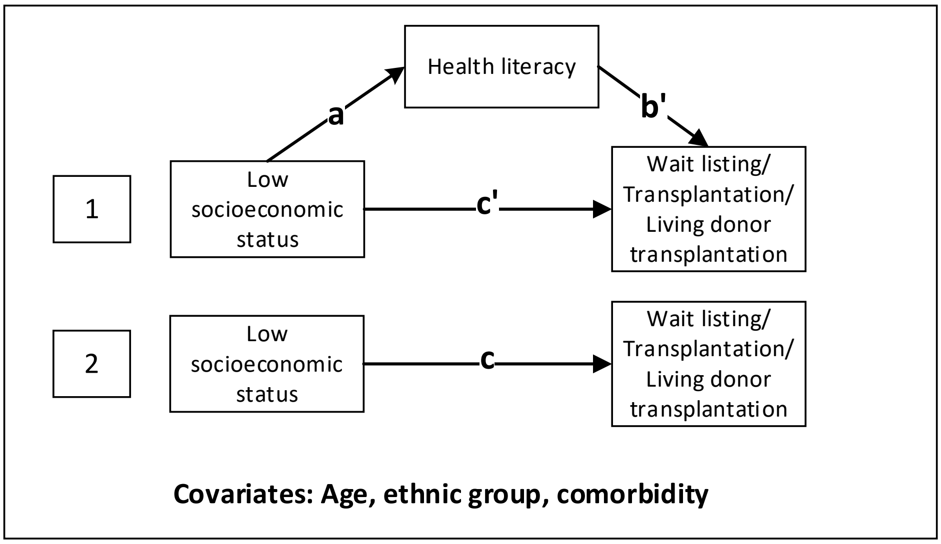


Figure 6-6: **Simplified model for health literacy as a mediator in the association between low socioeconomic status and access to transplantation**

Pathways to covariates shown in Figure 6-5 are implied but not shown.

In Figure 6-5 and Figure 6-6, pathway *c* indicates the known *total effect* of low SES on access to transplantation. Of note, in more detailed analysis of the effects of SES on access to transplantation in the ATTOM study, several markers of low SES including education, car ownership and accommodation are associated with reduced access to transplantation (Rishi Pruthi, personal communication). A proportion of this *total effect* of SES on access to transplantation is hypothesised to act via health literacy is a mediating pathway. This *indirect effect* is represented by pathways *a* and *b′.* The remaining *direct effect* of SES on access to transplantation (not mediated by health literacy) is represented by *c′.*

The aim of the following analysis is to explore this mediating relationship in order to establish if a significant mediating effect of health literacy exists, and to estimate its magnitude.

6.7.2 Methods

Standard methodology for mediation analysis[226] involves fitting statistical models for the four pathways illustrated in Figure 6-6, to calculate the coefficients *a, b′, c′* and *c,* as follows:

- *a* is the coefficient for the exposure (education) in a model with the mediator (health literacy) as the dependent variable, with adjustment for the covariates (age, ethnicity and comorbidity).
- *b′* is the coefficient for the mediator (health literacy) in a model with the outcome (transplantation) as the dependent variable, with adjustment for the exposure (education) and the covariates (age, ethnicity, comorbidity)
- *c′* is the coefficient for the exposure (education) in a model with the outcome (transplantation) as the dependent variable, with adjustment for the mediator (health literacy) and the covariates (age, ethnicity, comorbidity)
- *c* is the coefficient for the exposure (education) in a model with the outcome (transplantation) as the dependent variable, with adjustment for the covariates (age, ethnicity, comorbidity), but not for the mediator.

These are then used to estimate the direct, indirect and total effects in the model:

- The *direct effect* of the exposure (education) on the outcome (transplantation), not mediated by health literacy, is estimated by *c′.*
- The *indirect effect* of the exposure (education) on the outcome (transplantation), mediated by health literacy is calculated as *ab′* (or in some other cases as *a + b)*
- The *total effect* of education on transplantation can be estimated by *c*, but in this case is better estimated by *c′ + ab′* because of the presence of censored time-to-event data.[227]

6.7.2.1 Variable and statistical model choice

The original mediation methodology proposed by Barron and Kenny[228] uses linear regression models for all three pathways, so requires the mediator and outcome variables to fit the assumptions of linear regression. The health literacy and transplantation variables from ATTOM are not linear (they are time-to-event and ordinal variables) therefore changes in methodology are required:

a) Outcome (Time to wait-listing, time to transplantation, time to living-donor transplant)

When the outcome measure in a mediation model is expressed as time to event data, a 'survival' model is required to model pathways *b′* and *c′*. However, the use of a Cox proportional hazards model to perform the above analysis is not considered statistically sound,[229] and in simulation studies is inferior to other models. Gelfand et al. (2016)[227] instead propose the use of a Weibull accelerated failure time (AFT) model. The analysis presented here adapts the methodology from this paper, which uses the product (not sum) of covariates for pathways *a* and *b′* to estimate the indirect effect. It should be noted that AFT models report 'survival ratios', not hazard ratios as with proportional hazards models. Here, reported survival ratios indicate the ratio of time to transplant wait-listing or transplantation dependent on the binary exposure. A higher ratio indicates a longer time to the event (and reduced access to transplantation)

The specification of the time-to-event outcome variables is as in section 6.3.3, with one exception. Because the Weibull AFT model allows modelling of a time-to-event of zero days, patients who were wait-listed before dialysis start (or those receiving a living-donor transplant within 6 months of dialysis start without prior wait-listing) were included in the analysis of time to wait-listing presented here.

b) Exposure (Socioeconomic Status)

Multiple individual-level markers of low SES were recorded by ATTOM, including car and home ownership, education, marital status and employment. These measure individual facets of SES (Section 2.1) to indicate overall SES. A logical process whereby low SES might influence health literacy is via lower education (leading to lower general literacy and lower health literacy). A mediating effect of health literacy in the relationship between low educational level and outcomes has been tested elsewhere.[160] Therefore, low education was chosen as a marker of low SES. In a sensitivity analysis, another measure of SES, car ownership, was included as a covariate. This was to attempt to differentiate between the *overall* effect of SES on transplantation from the effect specific to education, although the close correlation between these markers of SES makes this differentiation difficult.

In order to allow intuitive interpretation of the results of mediation analysis, education has been specified as a binary variable, no educational qualifications (vs any).

c) Mediator (Health Literacy)

The ATTOM study used the SILS to measure health literacy on a five-point Likert scale (where 1 indicates highest health literacy and 5 indicates lowest health literacy, section 4.3). Other analyses in this thesis have used these scores to produce a binary variable for limited vs adequate health literacy. However, this analysis retains the original five-point variable (SILS responses) for two reasons. First, use of the five-point SILS response takes full advantage of the granularity of the data, increasing power to detect a mediating effect. Second, linear regression to calculate coefficient *a* allows calculation of the indirect effect by the product method, while using a binary mediator necessitates a more complex calculation.[230] Treating such Likert scale variables as linear is considered statistically valid by most, and treating them as categorical in mediation models is not recommended.[231] Therefore, SILS score was used as the mediating variable and a linear regression model was used to calculate covariate *a.*

d) Covariates

The covariates age, ethnic group (4 categories) and comorbidity by modified Charlson index (4 categories) were included in all models as described above. In a further sensitivity analysis, the mediation models were re-fitted for white subjects only. This was done to account for known interactions between ethnicity and SES which are relevant to dialysis populations in the UK.[232]

6.7.2.2 Modelling

Stata 14 (StataCorp LP, College station, TX, USA) was used in all analyses. The assumptions for the Weibull model were tested using log analysis time vs log survivor function plots. The Structural Equation Modelling command ‘gsem’ was used to fit the regression models and calculate the covariates *a, b′* and *c′*. The postestimation command ‘nlcom’ was used to calculate the indirect and total effects with 95% confidence intervals. Results of Weibull models were shown as coefficients and as equivalent time-to-event ratios. If both the total effect of education on the outcome (by *c′* + *ab′*) and the indirect effect via health literacy (*ab′*) were statistically significant, the proportion of the total effect mediated by health literacy was calculated.

6.7.3 Results

Plots of log analysis time vs log survivor function (Figure 6-7) for the three outcome variables time to wait-listing, time to living-donor transplant and time to any transplant showed no major violation of the Weibull assumption (as indicated by approximately straight plot lines[227])

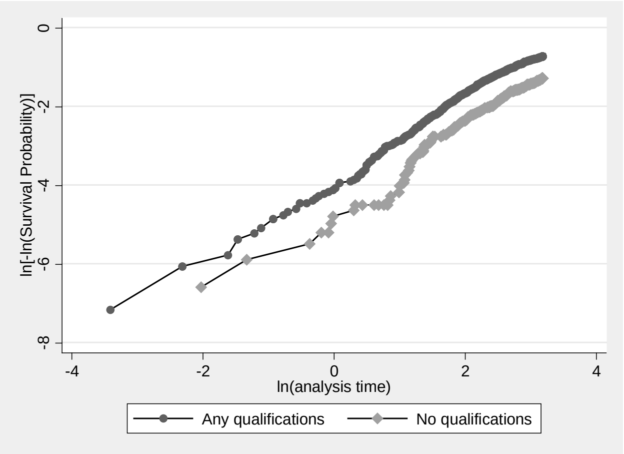
The results of mediation analysis for the three outcome variables are shown in Table 6-5, Table 6-6 and Table 6-7. Results from the individual models for pathways *a, b′, c′* and *c* are shown, which are then used to calculate the total effect of education on the outcome, the indirect effect via health literacy and the proportion of the total effect acting via the mediating pathway.

In the linear models for health literacy by SILS (*a*), no qualifications compared to any was associated with an increase in SILS score of 0.5 on the 5-point Likert scale (ie: lower health literacy). The overall effect of no qualifications on the outcomes (*c,* or more accurately calculated by $c' + ab$[227]) was statistically significant for all three outcome measures.

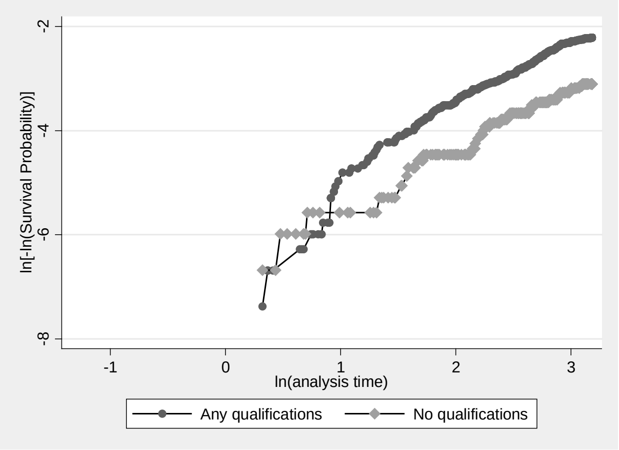
Patients with no educational qualifications had a 22% longer time to transplant wait-listing, 47% longer time to living-donor transplant and 35% longer time to transplant from any donor. Health literacy had a significant mediating effect in all cases, mediating 35%, 30% and 24% of the total effects respectively. The direct effect of no qualifications on wait-listing and living-donor transplantation (*c′*) is not statistically significant, likely to represent loss of statistical power.[226] This does not alter the significance of the overall results.

In sensitivity analyses (Appendices E.3 and E.4), addition of car ownership as a covariate resulted in a non-significant total effect of education on wait-listing and of education on time to living-donor transplant. There remained a significant total effect of education on time to transplant of any donor type, with significant mediation by health literacy. When only white patients were included, the total effect of education on wait-listing was no longer significant, but significant effects remained for time to living-donor transplant or transplant from any donor type, again with significant mediation by health literacy.

A: Time to wait-listing



B: Time to living-donor transplant



C: Time to any donor transplant

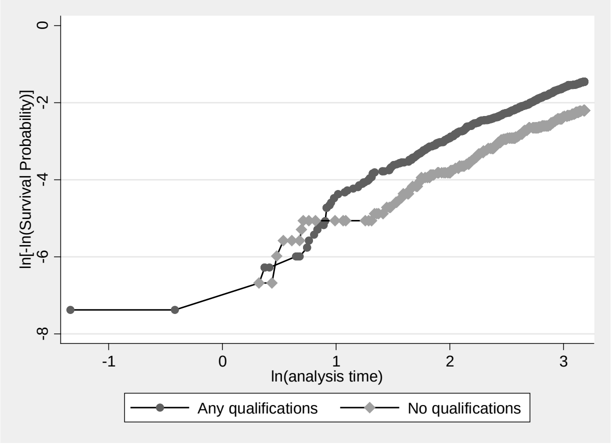


Figure 6-7: **Tests of the Weibull assumption for the three outcome variables**

Approximately straight lines indicate no major violation.

Table 6-5: Analysis of health literacy as a mediator of the effect of low educational level (no educational qualifications) on time to transplant wait-listing

Time to transplant wait-listing, n=2018	**Path/effect**	**Estimate (95% CI)**	**Time-to-event ratio (95% CI)**	**P**
Linear Regression				
	a no qualifications->lower health literacy	0.50 0.39,0.61)	-	**<0.001**
Weibull model 1				
	c no qualifications->wait-listing (model excludes health literacy)	0.21 (0.02,0.39)	1.23 (1.02,1.48)	**0.030**
Weibull model 2				
	b’ health literacy->wait-listing	0.14 (0.07,0.22)	1.15 (1.07,1.25)	**<0.001**
	c’ no qualifications->wait-listing (model includes health literacy)	0.13 (-0.67,0.32)	1.14 (0.94,1.38)	0.2
Calculate direct/indirect effects				
	Indirect effect (ab’)	0.07 (0.03,0.11)	1.07 (1.03,1.12)	**0.001**
	Total effect (by c’ +ab’)	0.20 (0.02,0.39)	1.22 (1.02,1.48)	**0.033**
	Proportion mediated		**35%**	

Table 6-6: Analysis of health literacy as a mediator of the effect of low educational level (no educational qualifications) on time to living-donor transplant

Time to living-donor transplant, n=2393	**Path/effect**	**Estimate (95% CI)**	**Time-to-event ratio (95% CI)**	**P**
Linear Regression				
	a no qualifications->lower health literacy	0.52 (0.42,0.62)	-	**<0.001**
Weibull model 1				
	c no qualifications->transplantation (model excludes health literacy)	0.36 (0.02,0.70)	1.43 (1.01,2.02)	**0.040**
Weibull model 2				
	b’ health literacy-> transplantation	0.22 (0.06,0.39)	1.25 (1.06,1.47)	**0.007**
	c’ no qualifications-> transplantation (model includes health literacy)	0.27 (-0.72,0.62)	1.31 (0.93,1.85)	0.1
Calculate direct/indirect effects				
	Indirect effect (ab’)	0.12 (0.03,0.20)	1.12 (1.03,1.23)	**0.010**
	Total effect (by c’ +ab’)	0.39 (0.04,0.73)	1.47 (1.04,2.08)	**0.027**
	Proportion mediated		**30%**	

Table 6-7: Analysis of health literacy as a mediator of the effect of low educational level (no educational qualifications) on time to transplant from any donor type

Time to any transplant, n=2390	Path/effect	Estimate (95% CI)	Time-to-event ratio (95% CI)	P
Linear Regression				
	a no qualifications->lower health literacy	0.52 (0.41,0.62)	-	**<0.001**
Weibull model 1				
	c no qualifications-> transplantation (model excludes health literacy)	0.29 (0.09,0.48)	1.33 (1.09,1.62)	**0.005**
Weibull model 2				
	b’ health literacy-> transplantation	0.14 (0.05,0.22)	1.15 (1.05,1.25)	**0.002**
	c’ no qualifications-> transplantation (model includes health literacy)	0.23 (0.27,0.43)	1.25 (1.03,1.53)	**0.026**
Calculate direct/indirect effects				
	Indirect effect (ab’)	0.07 (0.02,0.12)	1.07 (1.02,1.12)	**0.003**
	Total effect (by c’ +ab’)	0.30 (0.10,0.50)	1.35 (1.10,1.64)	**0.003**
	Proportion mediated		**24%**	

6.7.4 Discussion

This novel analysis demonstrates the effect of health literacy as a mediator between SES and access to kidney transplantation. The results suggest socioeconomic inequity in the process of receiving deceased- and living-donor transplants, which results in inequity in access to any transplant. This process appears to be mediated in part by health literacy, with health literacy differences accounting for around a third of the total effect.

Health literacy has been shown in this thesis to be associated with lower educational level. This is likely to reflect the effect of general literacy skills on improving health literacy. However, there are likely to be other mechanisms by which low SES associates with low health literacy. These include lower social status, lack of confidence in clinician-patient interactions and lack of support networks. An analysis with car ownership as an added covariate aimed to differentiate between the effects of low education and other effects of low SES. In this analysis, the apparent overall effect of education on wait-listing or living-donor transplantation was no longer significant, but a significant effect on time to any transplant remained. The outcome variable for time to any transplant has a larger number of events, and the analysis excludes fewer subjects. As such, the loss of significance for time to wait-listing and time to living-donor transplantation in this sensitivity analysis could relate to loss of statistical power to detect a difference. A further sensitivity analysis which included only white patients showed no significant effect of education on transplant wait-listing but did show significant effects of time to living-donor transplantation and time to transplant from any donor type. This analysis confirms that differences in SES by ethnicity are not the sole cause of the apparent inequity in access to transplantation, at least for the process of living-donor transplantation.

Potential mechanisms by which health literacy could influence access to the deceased-donor transplant list and to living-donor transplantation are discussed in section 6.6. In this mediation analysis, the largest effect was that of education on time to living-donor transplant: around a 50% increase in time to transplant for those with no educational qualifications, with a third of this effect mediated by health literacy. The process of access to living-donor transplantation presents specific challenges in communication for the potential recipient. These include understanding of the complex process of donor and recipient preparation, communication of the advantages of living-donor transplantation to potential donors, the ability of the donors to understand these benefits, and barriers to donation for a potential donor.

There is some other evidence of health literacy as a mediator in the relationship between SES and health outcomes. One study used path analysis and measurement of overall model fit to identify a significant mediating effect of health literacy in the relationship between low educational level and diabetes control.[160] Another study compared the effect of low education on lower health status with and without adjustment for health literacy, concluding that health literacy has a significant mediating effect in this relationship.[159]

In addition to the benefits listed in section 6.6, this mediation analysis benefits from a statistical model which investigates not just associations between health literacy and transplantation, but the causal pathways which underlie this relationship. Although the techniques of mediation analysis have been available for many years, their application in healthcare research has not been widespread. The analysis also calls upon recent literature to use appropriate techniques for investigating mediation with a time-to-event outcome. There are further limitations specific to this mediation analysis:

- The mediation models rely on assumptions relating to two types of regression model, as well as assumptions that the proposed relationships contained within the overall model accurately reflect true relationships.
- There is a lack of consensus on the optimal techniques for mediation analysis in general. Alternative methodology includes the use of counterfactuals to calculate the direct and indirect effects[233], inverse odds ratio weighting,[234, 235] semiparametric models,[236]the use of Structural Equation Modelling with measurement of overall model fit,[160] and non-parametric machine learning models.[237] Ideally, alternative methods would have been

explored as sensitivity analyses. This is outside the scope of the analysis presented here, but is planned as future work.

- Differing techniques for mediation analysis with a time-to-event outcome have also been used. The analyses presented here use a Weibull AFT model in preference over a Cox model as recommended in Gelfand et al. [227] Other authors have used an Aalen additive hazard model and reported superiority over Cox models.[235] These will be explored in future work, with support from experts in this specialist field of statistics.
- The models treat the health literacy variable (SILS score) as continuous. Although this model is considered statistically sound,[231] more complex modelling techniques using ordered logistic regression,[238] should be explored in future work.
- The large number of variables and associations tested in the models reduce the power to detect associations.
- These analyses, using observational data, provide evidence in support of health literacy as a mediator in the relationship between low SES and deceased- or living-donor transplantation, but do not prove causation.

The findings of this mediation analysis have implications for the design of clinical services practice. If health literacy truly mediates a significant proportion of the effect of low SES on transplant access, then interventions which effectively eliminate the effects of health literacy differences could significantly reduce inequity. However, the optimal design for such interventions is unclear. This is discussed further in the concluding chapter.

Chapter 7: Conclusions

7.1 Main findings

- A systematic review including data from over 12,000 patients with CKD, predominantly from the USA found that limited health literacy was associated with low SES, high comorbidity and non-white ethnicity (Section 3.3)
- UK data showed that limited health literacy was independently associated with higher comorbidity and several markers of low SES (Chapter 5)
- By meta-analysis, the pooled prevalence of limited health literacy was lower among transplanted patients compared to those with non-dialysis CKD or on dialysis (Section 3.3)
- In UK patients with CKD, the prevalence of limited health literacy was reduced among wait-listed and transplanted patients compared to those starting dialysis. The lowest prevalence of limited health literacy were seen among recipients of pre-emptive or living-donor transplants. (Chapter 5)
- A systematic review of health literacy and patient outcomes in CKD (Section 3.4) found a large variety of outcomes tested for association with health literacy. The quality of evidence was low, with few cohort studies, mostly in dialysis populations. No prospective studies investigated the effect of health literacy on access to transplantation. Findings from cohort studies included:
    - Independent associations between low heath literacy and hospital admissions (dialysis and non-dialysis CKD) or cardiovascular events (non-dialysis CKD)
    - Independent associations between low health literacy and mortality in USA and international dialysis populations.
- Prospective analysis of UK data (Chapter 6) showed no independent associations between limited health literacy and survival on dialysis, dialysis quality, dialysis access, dialysis modality, peritoneal dialysis failure, transplant function or transplant failure. Significant associations were found between limited health literacy and reduced time to transplant wait-listing, living-donor transplantation or transplantation from any donor type, after adjustment for demographics, comorbidity and PRD (but without SES adjustment). Increased time to deceased-donor transplantation among those with limited health literacy appears to relate to increased time to wait-listing: there was no difference in time from wait-listing to deceased-donor transplant allocation.
- In a mediation analysis, health literacy appeared to have a significant mediating effect in the pathway from low SES (as reduced educational level) to deceased-donor transplant

wait-listing, transplantation from any donor type and living-donor transplantation. These results may suggest that health literacy differences promote socioeconomic inequity in access to living- and deceased-donor kidney transplantation

7.2 Implications for clinical practice and future research

Clinicians should be aware that at least a quarter of patients with CKD have limited health literacy. By definition, this represents an inadequate level of health literacy to facilitate successful care when standard communication methods are used. Unfortunately, poor health literacy is more likely to affect patients with an increased burden of disease, and with other factors which reduce their capacity to cope with disease and its treatment.[239] This appears to result in reduced access to deceased- and living-donor transplantation among those with limited health literacy.

Although many of the mechanisms which generate socioeconomic inequity in CKD care are outside the control of the clinician, the role of health literacy in mediating the effect of SES on pathways to transplantation may be modifiable. Standard shared decision-making and self-management initiatives may not be suitable for those with lower health literacy,[240, 241] and changes in clinical practice may be necessary. Based on current evidence and recommendations, clinicians may consider taking up ‘universal precautions’ to improve communication with patients, including techniques such as ‘teachback’.[239, 242] However, global adoption of these changes in communication methods may be limited because of resistance from clinicians in altering practice without evidence of improvement in clinical outcomes. A more effective approach to reduce the negative effects of low health literacy on access to transplantation may be the development and testing of educational interventions. Some educational interventions have already been successful in improving knowledge and self-management developed in CKD,[243] although health literacy and transplant access have not been specifically targeted. A successful intervention in this setting would improve patients’ understanding of the transplantation process, and promote activities leading to early deceased-donor transplant wait-listing, and living-donor transplantation. Secondary benefits may include improved patient satisfaction and cost-effectiveness. Such interventions would be ‘complex’, and should be developed with reference to established guidelines such as the Medical Research Council Complex Interventions Framework. [244] This guidance is illustrated in Figure 7-1.

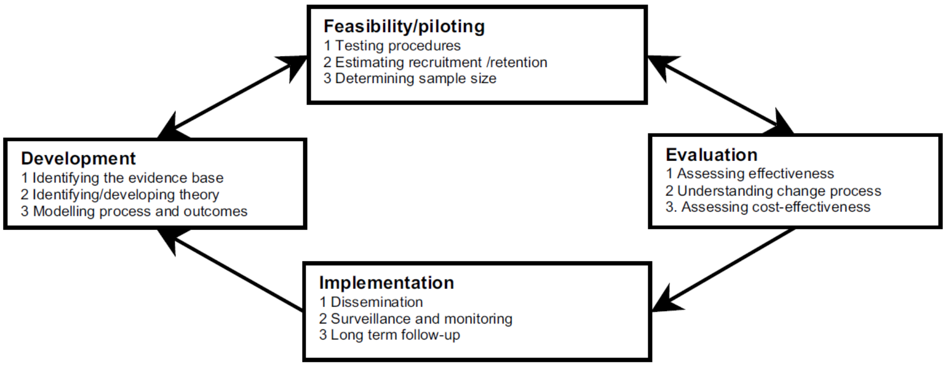


Figure 7-1: Key elements of the development and evaluation process of a complex intervention

From Medical Research Council updated guidance on complex interventions.[244]

The results presented in this thesis represent some of the preliminary work required to develop such an intervention ('Development' points 1 and 2). Patients with low health literacy have been identified as a potential target for an intervention aiming to improve access to deceased- and living-donor transplantation. Theoretical pathways in which health literacy could interact with SES to affect transplant access have been explored in mediation analysis. These results have been disseminated in this thesis and associated publications and presentations. Immediate future work will include further presentation publication of results from Chapter 6, and analysis of associations of limited health literacy with healthcare expenditure using linked Hospital Episodes Statistics data, which may illustrate health economic benefits of changes in clinical practice to improve understanding among those with lower health literacy.

The next steps in the process of intervention development include analysing existing interventions relevant to health literacy and CKD to inform intervention design. A current systematic review of interventions to improve health literacy in people with CKD may be helpful,[19] although systematic review of literature performed for this thesis did not identify many such interventions. Systematic reviews of educational interventions for those with low health literacy in other healthcare settings have shown potential to improve outcomes,[245, 246] but none have focussed on CKD populations. The outcomes tested in these interventions include some of the 'patient attributes' and 'processes of care' identified in studies in section 3.4, in addition to 'hard' clinical outcomes. Evaluation of a health literacy-related intervention to improve access to deceased- or living-donor transplantation could measure some of these intermediate factors, but its efficacy should be measured primarily by improvements in endpoints such as time to transplant wait-listing or time to transplantation.

Intervention design will be informed by a closer view of the effect of poor health literacy as a potential barrier to transplant wait-listing and living-donor transplantation. This should include qualitative investigation of current communication methods in clinical practice[247] to identify areas where deficits in communication could impact on outcomes. The communication processes resulting in deceased-donor transplant wait-listing and living-donor transplantation should be explored separately. In the case of living-donor transplantation, interactions between clinicians, potential recipients and potential donors may also be important, and the health literacy of potential donors should be considered. The attitudes of clinicians to patients with lower health literacy should also be assessed: clinicians may perceive that patients with low health literacy are uninterested in their care.

Potential intervention designs include training for all clinicians in health literacy-sensitive communication methods, educational tools and decision-aids, or targeted educational sessions with patients to allow effective participation in decision-making. Some have advocated screening for low health literacy in clinical practice, with provision of interventions only to those with limited health literacy, but this may risk stigmatising patients.[248] Evidence-based consensus on the optimal tools to measure health literacy in clinical and research practice would enable easier comparison of results from future research. Measurement of health literacy in routine clinical practice could extend current work in the ‘Think Kidneys’ initiative (NHS England and the UK Renal Registry)[249] studying patient experience, activation and patient-reported outcomes. Interactions between health literacy and other patient attributes such as capacity[146] and patient activation[143] should be considered. 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. Randomised trials have been performed for health literacy-sensitive interventions in diabetes[250], and for an intervention to improve knowledge of transplantation among Hispanic populations[251]

In summary, this thesis presents a significant expansion of the knowledge of the prevalence, associations and apparent effects of low health literacy in CKD populations. Novel research using data from the ATTOM study represents the first large scale health literacy research in UK patients with CKD. Trends in the prevalence of limited health literacy and its associations with socioeconomic and demographic factors from the USA have been confirmed in the UK CKD population. Independent associations between reduced health literacy and reduced access to the deceased-donor waiting list, and to living-donor transplantation were demonstrated, and mediation analysis demonstrated evidence of health literacy as a promoter of health inequity in these processes. Future research should focus on applying these findings to promote evidence-based changes in clinical practice with the aim of reducing inequity and improving clinical outcomes.

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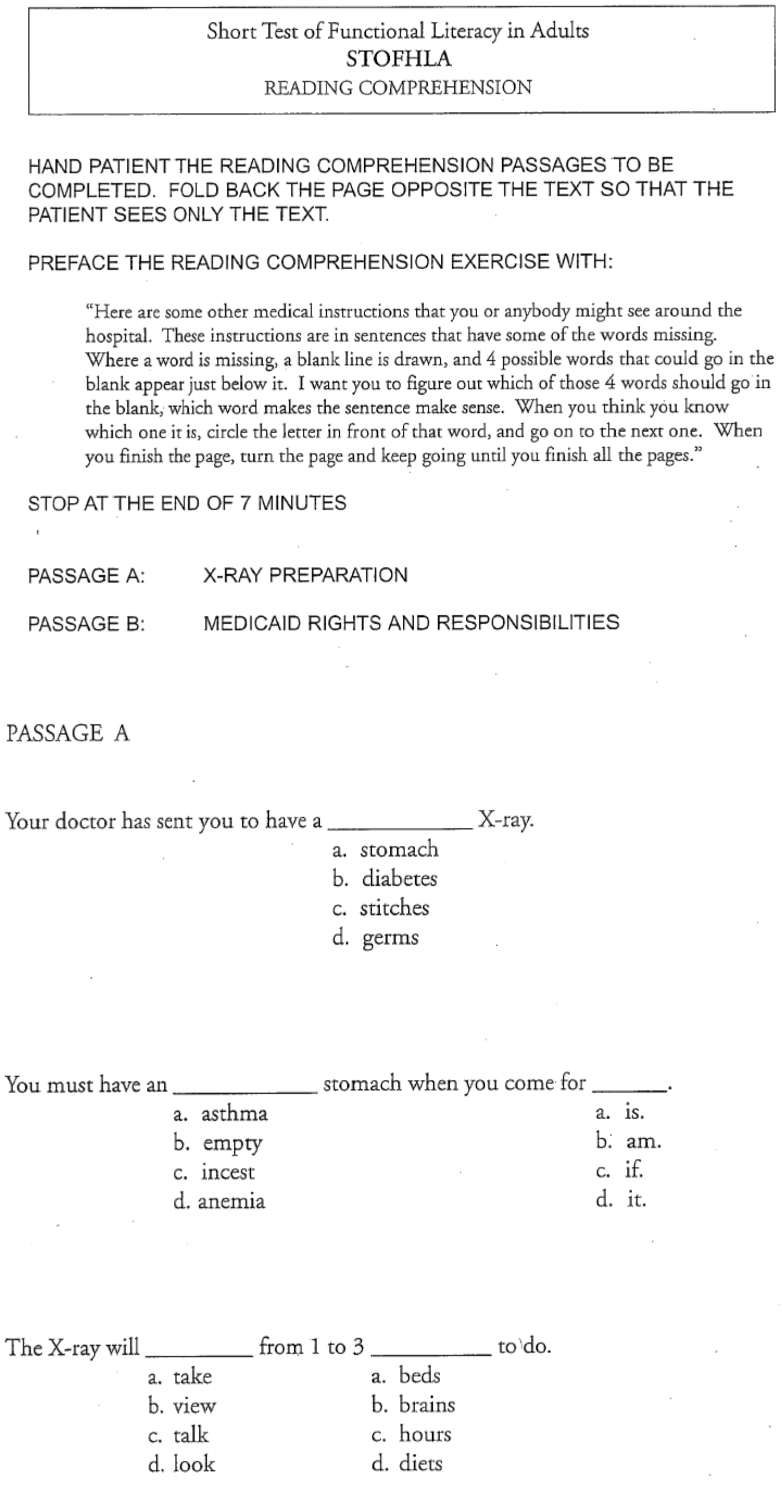
Appendix A Examples of health literacy measures (Chapter 2)

A.1 Short Test of Functional Health Literacy in Adults (STOFHLA)



Short Test of Functional Literacy in Adults
STOFHLA
READING COMPREHENSION

HAND PATIENT THE READING COMPREHENSION PASSAGES TO BE COMPLETED. FOLD BACK THE PAGE OPPOSITE THE TEXT SO THAT THE PATIENT SEES ONLY THE TEXT.

PREFACE THE READING COMPREHENSION EXERCISE WITH:

> "Here are some other medical instructions that you or anybody might see around the hospital. These instructions are in sentences that have some of the words missing. Where a word is missing, a blank line is drawn, and 4 possible words that could go in the blank appear just below it. I want you to figure out which of those 4 words should go in the blank, which word makes the sentence make sense. When you think you know which one it is, circle the letter in front of that word, and go on to the next one. When you finish the page, turn the page and keep going until you finish all the pages."

STOP AT THE END OF 7 MINUTES

PASSAGE A: X-RAY PREPARATION

PASSAGE B: MEDICAID RIGHTS AND RESPONSIBILITIES

PASSAGE A

Your doctor has sent you to have a ____________ X-ray.

a. stomach
b. diabetes
c. stitches
d. germs

You must have an ____________ stomach when you come for ______.

a. asthma   a. is.
b. empty   b. am.
c. incest   c. if.
d. anemia   d. it.

The X-ray will _________ from 1 to 3 __________ to do.

a. take   a. beds
b. view   b. brains
c. talk   c. hours
d. look   d. diets

THE DAY BEFORE THE X-RAY.

For supper have only a ____________ snack of fruit, ___________ and jelly,

a. little
b. broth
c. attack
d. nausea

a. toes
b. throat
c. toast
d. thigh

with coffee or tea.

After _____________ , you must not ________ or drink

a. minute,
b. midnight,
c. during,
d. before,

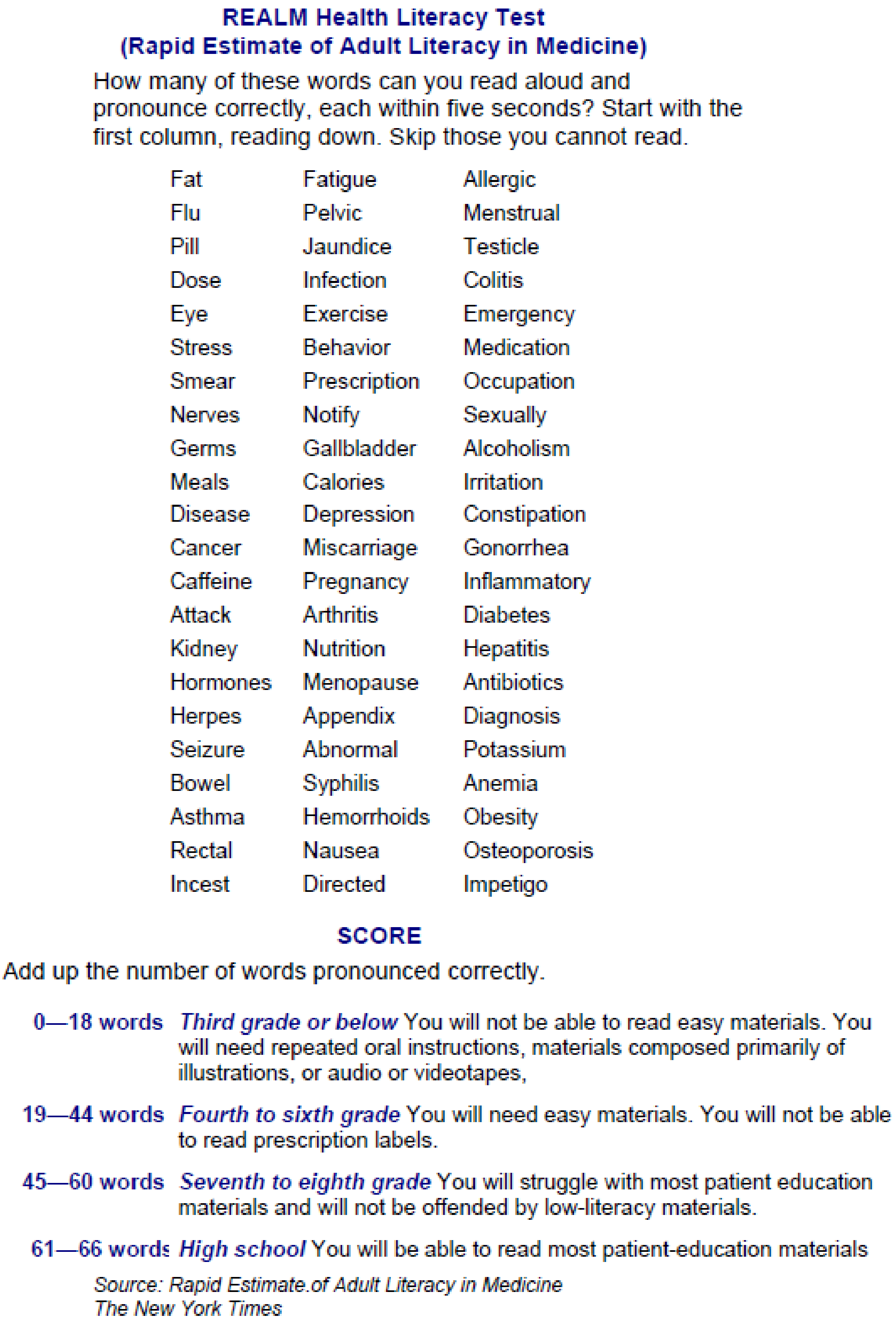
a. easy
b. ate
c. drank
d. eat

anything at ________ until after you have ________ the X-ray.

a. ill
b. all
c. each
d. any

a. are
b. has
c. had
d. was

A.2 Rapid Estimate of Adult Literacy in Medicine (REALM)



REALM Health Literacy Test
(Rapid Estimate of Adult Literacy in Medicine)

How many of these words can you read aloud and pronounce correctly, each within five seconds? Start with the first column, reading down. Skip those you cannot read.

Fat
Flu
Pill
Dose
Eye
Stress
Smear
Nerves
Germs
Meals
Disease
Cancer
Caffeine
Attack
Kidney
Hormones
Herpes
Seizure
Bowel
Asthma
Rectal
Incest

Fatigue
Pelvic
Jaundice
Infection
Exercise
Behavior
Prescription
Notify
Gallbladder
Calories
Depression
Miscarriage
Pregnancy
Arthritis
Nutrition
Menopause
Appendix
Abnormal
Syphilis
Hemorrhoids
Nausea
Directed

Allergic
Menstrual
Testicle
Colitis
Emergency
Medication
Occupation
Sexually
Alcoholism
Irritation
Constipation
Gonorrhea
Inflammatory
Diabetes
Hepatitis
Antibiotics
Diagnosis
Potassium
Anemia
Obesity
Osteoporosis
Impetigo

SCORE

Add up the number of words pronounced correctly.

0—18 words *Third grade or below* You will not be able to read easy materials. You will need repeated oral instructions, materials composed primarily of illustrations, or audio or videotapes,

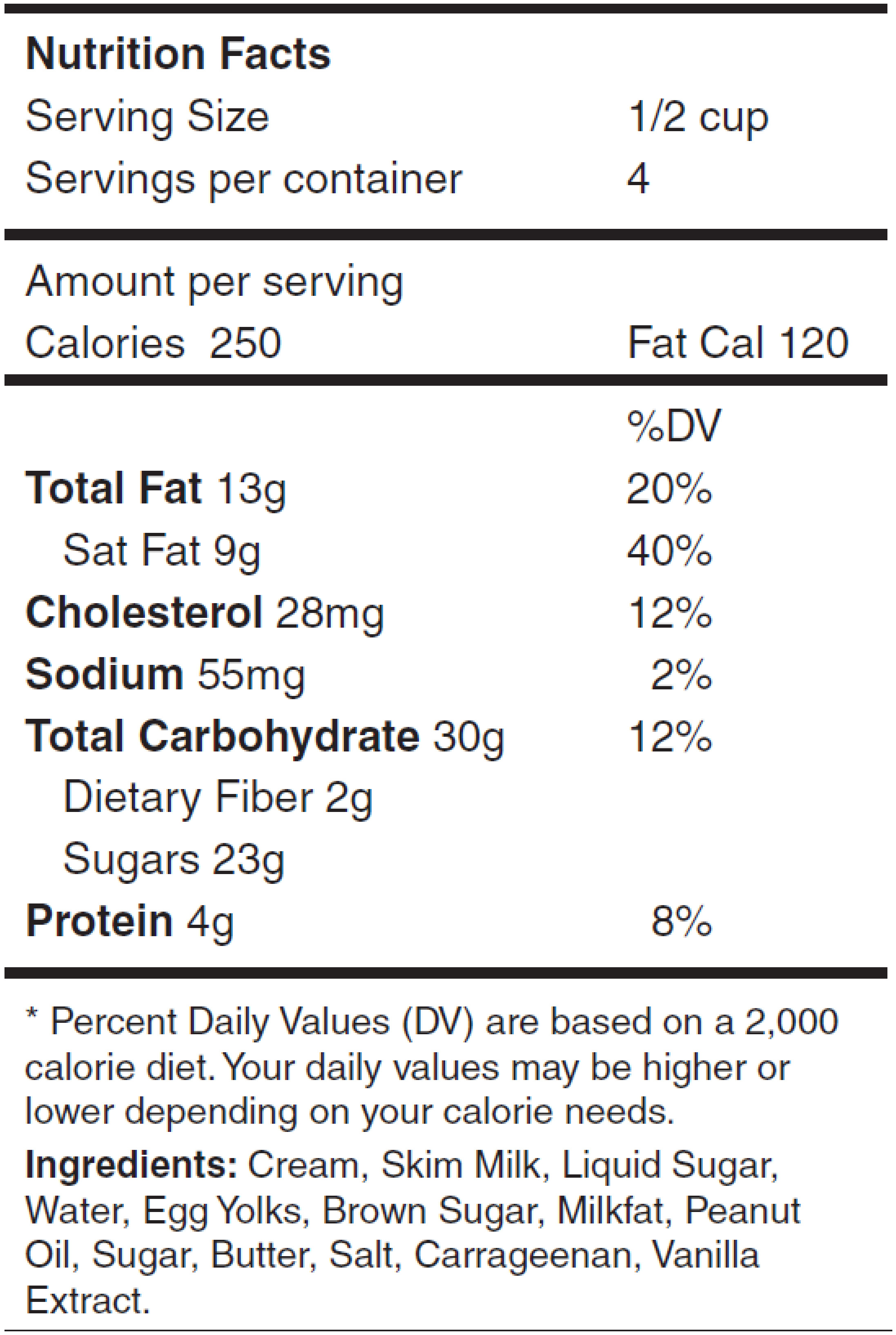
19—44 words *Fourth to sixth grade* You will need easy materials. You will not be able to read prescription labels.

45—60 words *Seventh to eighth grade* You will struggle with most patient education materials and will not be offended by low-literacy materials.

61—66 words *High school* You will be able to read most patient-education materials

Source: Rapid Estimate.of Adult Literacy in Medicine
The New York Times

A.3 Newest Vital Sign (NVS)



Nutrition Facts

Serving Size	1/2 cup
Servings per container	4
Amount per serving	
Calories 250	Fat Cal 120
	%DV
Total Fat 13g	20%
Sat Fat 9g	40%
Cholesterol 28mg	12%
Sodium 55mg	2%
Total Carbohydrate 30g	12%
Dietary Fiber 2g	
Sugars 23g	
Protein 4g	8%

* Percent Daily Values (DV) are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

Ingredients: Cream, Skim Milk, Liquid Sugar, Water, Egg Yolks, Brown Sugar, Milkfat, Peanut Oil, Sugar, Butter, Salt, Carrageenan, Vanilla Extract.

	ANSWER CORRECT?	
	YES	NO

READ TO SUBJECT: This information is on the back of a container of a pint of ice cream.

QUESTIONS

1. If you eat the entire container, how many calories will you eat?

Answer ☐ 1,000 is the only correct answer ________ ________

2. If you are allowed to eat 60 g of carbohydrates as a snack, how much ice cream could you have?

Answer Any of the following is correct: ________ ________

☐ 1 cup (or any amount up to 1 cup)

☐ Half the container

Note: If patient answers "2 servings," ask "How much ice cream would that be if you were to measure it into a bowl?"

3. Your doctor advises you to reduce the amount of saturated fat in your diet. You usually have 42 g of saturated fat each day, which includes 1 serving of ice cream. If you stop eating ice cream, how many grams of saturated fat would you be consuming each day?

Answer 33 is the only correct answer ________ ________

4. If you usually eat 2500 calories in a day, what percentage of your daily value of calories will you be eating if you eat one serving?

Answer 10% is the only correct answer ________ ________

Pretend that you are allergic to the following substances: Penicillin, peanuts, latex gloves, and bee stings.

5. Is it safe for you to eat this ice cream?

Answer ☐ No ________ ________

6. (Ask only if the patient responds "no" to question 5): Why not?

Answer Because it has peanut oil. ________ ________

Total Correct ________

Appendix B Additional material for systematic reviews (Chapter 3)

B.1 Search terms

B.1.1 Search terms for Medline, Embase and Ovidfulltext (via OvidSP)

1. (Health adj3 litera*).tw.
2. (literacy or literate).tw.
3. HL.tw
4. Health Education/
5. Consumer Health Information/
6. educational status/
7. Patient Education as Topic/
8. Health Knowledge, Attitudes, Practice/
9. comprehension/
10. Patient Education.tw.
11. or/3-10
12. and/2,11
13. numeracy.tw.
14. Wide Range Achievement Test.tw.
15. Rapid Estimate of Adult Literacy in Medicine.tw.
16. Peabody Individual Achievement Test.tw.
17. Slosson oral reading test.tw.
18. National Adult Reading Test.tw.
19. (Woodcock-Johnson and test).tw.
20. (medical terminology and achievement).tw.
21. literacy assessment for diabetes.tw.
22. adult basic education test.tw.
23. Newest Vital Sign.tw.
24. Short Assessment of Health Literacy.tw.
25. Health literacy Screening Question Methodologies.tw.
26. Single-Item Literacy Screener.tw.
27. Health Literacy Skills Instrument.tw.
28. Medical Term Recognition Test.tw.

29. Short Literacy Survey.tw.
30. Brief Health literacy Screen.tw.
31. or/14-30
32. (SORT and read).tw.
33. (REALM and read).tw.
34. (MART and read).tw.
35. TOFHLA.tw.
36. STOFHLA.tw.
37. WRAT.tw.
38. PIAT.tw.
39. NART.tw.
40. AMNART.tw.
41. NVS.tw.
42. SAHLSA.tw.
43. HLSQM.tw.
44. SILS.tw.
45. HLSI.tw.
46. HLSI-SF.tw.
47. METER.tw.
48. SAHL-S&E.tw.
49. SLS.tw.
50. BHLS.tw.
51. or/32-50
52. and/2,51
53. 1 or 12 or 13 or 31 or 52
54. Kidney diseases/
55. exp Renal replacement therapy/
56. renal insufficiency/
57. exp renal insufficiency, chronic/
58. renal replacement therapy/
59. dialysis.tw.
60. (hemodialysis or haemodialysis).tw.
61. (hemofiltration or haemofiltration).tw.
62. (hemodiafiltration or haemodiafiltration).tw.

63. peritoneal dialysis/
64. (peritoneal and dialysis).tw.
65. (kidney disease* or renal disease* or kidney failure or renal failure).tw.
66. (ESRF or ESKF or ESRD or ESKD).tw.
67. (CKF or CKD or CRF or CRD).tw.
68. (CAPD or CCPD or APD).tw.
69. (predialysis or pre-dialysis).tw.
70. Kidney transplantation/
71. (renal transplant* or kidney transplant*).tw.
72. or/54-71
73. and/53,72

B.1.2 Search Strategy for Health Management Information Consortium , Cinahl, Psychinfo (via NICE Healthcare databases)

1. (Health adj3 litera*).tw
2. (literacy OR literate).tw
3. HL.tw
4. HEALTH EDUCATION/
5. CONSUMER HEALTH INFORMATION/
6. EDUCATIONAL STATUS/
7. PATIENT EDUCATION/
8. ATTITUDES/ OR KNOWLEDGE/
9. COMPREHENSION/
10. Patient AND Education.tw
11. 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
12. 2 AND 11
13. numeracy.tw
14. Wide AND Range AND Achievement AND Test.tw
15. Rapid AND Estimate AND of AND Adult AND Literacy AND in AND Medicine.tw
16. Peabody AND Individual AND Achievement AND Test.tw
17. Slosson AND oral AND reading AND test.tw
18. National AND Adult AND Reading AND Test.tw
19. (Woodcock-Johnson AND test).tw
20. (medical AND terminology AND achievement).tw
21. literacy AND assessment AND for AND diabetes.tw
22. adult AND basic AND education AND test.tw
23. Newest AND Vital AND Sign.tw
24. Short AND Assessment AND of AND Health AND Literacy.tw
25. Health AND literacy AND Screening AND Question AND Methodologies.tw
26. Single-Item AND Literacy AND Screener.tw
27. Health AND Literacy AND Skills AND Instrument.tw
28. Medical AND Term AND Recognition AND Test.tw
29. Short AND Literacy AND Survey.tw
30. Brief AND Health AND literacy AND Screen.tw
31. 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30
32. (SORT AND read).tw
33. (REALM AND read).tw
34. (MART AND read).tw
35. TOFHLA.tw
36. STOFHLA.tw
37. WRAT.tw
38. PIAT.tw
39. NART.tw
40. AMNART.tw
41. NVS.tw
42. SAHLSA.tw
43. HLSQM.tw
44. SILS.tw
45. HLSI.tw
46. HLSI-SF.tw
47. METER.tw
48. SAHL-SandE.tw
49. SLS.tw
50. BHLS.tw
51. 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50
52. 2 AND 51
53. 1 OR 12 OR 13 OR 31 OR 52
54. KIDNEY DISEASES/
55. ((renal replacement therapy)).af
56. dialysis.tw
57. (hemodialysis OR haemodialysis).tw
58. (hemofiltration OR haemofiltration).tw
59. (hemodiafiltration OR haemodiafiltration).tw
60. PERITONEAL DIALYSIS/
61. (peritoneal AND dialysis).tw
62. (kidney AND disease* OR renal AND disease* OR kidney AND failure OR renal AND failure).tw
63. (ESRF OR ESKF OR ESRD OR ESKD).tw
64. (CKF OR CKD OR CRF OR CRD).tw
65. (CAPD OR CCPD OR APD).tw
66. (predialysis OR pre-dialysis).tw
67. KIDNEY TRANSPLANTS/
68. (renal AND transplant* OR kidney AND transplant*).tw
69. exp KIDNEY DISEASES/
70. exp RENAL SERVICES/ OR exp KIDNEY DISEASES/ OR exp KIDNEY TRANSPLANTS/ OR exp HAEMODIALYSIS/
71. 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70
72. 53 AND 71

B.2 Sensitivity analysis: inclusion of conference abstracts (for prevalence and associations Systematic review, Section 3.2

In a sensitivity analysis, searches were widened to include conference abstracts. 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 original database searches. Abstracts 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'. The UK Health Literacy Network[252] and Health Literacy Research Conferences[253] 2011-2016 were searched for CKD-related terms.

Sixty conference abstracts were identified by these searches. These included 14 studies of more than 50 patients with CKD. Eleven of these used a validated health literacy measure and provided a prevalence value for limited health literacy, so were included in this sensitivity analysis and summarised inTable B.2.1.

Conference abstracts were analysed along with the 20 studies included in the primary analysis. Of 31 studies, 19 were cross-sectional surveys, eight used baseline data from cohort studies, three used baseline data from clinical trials and one was a review of patient notes where health literacy was measured during routine care. One study presented UK data, one from multiple countries (), one from New Zealand and 28 from the USA. Study quality was low for 24 studies and moderate for seven studies.

In total, 25,532 patients were studied, including 1,405 patients included in the 2012 review. This included 4,903 patients with non-dialysis CKD from 13 studies, 17,125 dialysis patients from 15 studies, and 2,560 transplant patients from 5 studies. Five studies included patients from multiple treatment stages. Limited health literacy prevalence by treatment stage was not available for 946 patients from two studies,[179, 180] even after communication with the authors. Studies included a median of 170 patients (IQR: 107-330.5). The median prevalence of limited health literacy by study was 23% (IQR: 16-35%). The overall pooled prevalence of limited health literacy was 25.2% (95% CI: 21.7-28.6%). A high degree of heterogeneity was present between studies (I^2 =97.5%). Pooled prevalence of limited health literacy was 25.1% (95% CI: 19.0-31.3) among patients with non-dialysis CKD, 24.9% (95% CI: 20.5-29.2) among dialysis patients, and 13.6% (95% CI: 6.5-20.6) among transplant patients. Overall, there was significant between-group heterogeneity (p=0.02), although this appears to be related to the lower prevalence of limited health literacy in transplant patients: when patients with non-dialysis CKD and dialysis patients were compared separately, no significant between-group heterogeneity was present (p=0.95).

Univariate meta-regression analysis by proportion of non-white patients and mean or median patient age showed that higher proportion of non-white participants was associated with higher limited health literacy prevalence (ß:0.31; 95% CI: 0.1,0.5; p=0.005), although significant residual between-study heterogeneity was present. Age of study participants was not significantly associated with the prevalence of limited health literacy (ß:0.38; 95% CI: -0.6,1.4; p=0.4).

B.2.1 Characteristics of conference abstracts meeting the inclusion criteria.

Outcome variables are listed only if statistical models included health literacy as an exposure variable. * Studies included in Fraser 2012 review. α Frequencies from personal communication with the authors β- Australia, New Zealand, Canada, UK, USA, Belgium, France, Countries of the former Gulf Cooperation Council', Germany, Italy, Japan, Russia, Span, Sweden, and Turkey.

CKD- Chronic Kidney Disease; HD- Haemodialysis; PD- Peritoneal Dialysis; CV- Cardiovascular; CVD: Cardiovascular disease; BP-Blood Pressure; BMI- Body Mass Index; MAP- Mean Arterial Pressure; DBP- Diastolic Blood Pressure; PVD- Peripheral Vascular Disease; LDR-Living-donor recipient; DDR- deceased-donor recipient; AKI- Acute Kidney Injury; MDRD: Modification of Diet in Renal Disease; CPR: Cardiopulmonary resuscitation; ED- Emergency Department; LDL- Low density lipoprotein; SES- Socioeconomic status

Study Year Location	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Design	Setting & recruitment method	Participants	Exclusion criteria	Health literacy measure	Outcome variables tested	Limited health literacy prevalence (%)
Blandon [198] 2011 USA	225	-	49	Non-dialysis CKD 2-4	Health literacy and BP control in Hispanic Americans	Cross-sectional	Adults from nephrology outpatients clinic	91% Hispanic 73% low income 61% diabetic	None stated	STOFHLA (English /Spanish)	BP control	46
Cavanaugh 3*[199] 2010 USA	50	[51]	48	Prevalent HD	Association of health literacy and type of dialysis access used	Cross-sectional	Adults from a single dialysis unit	74% black 33% dialysis catheter	Not stated	REALM	Dialysis catheter use	32
Cavanaugh 4 [190] 2015 Multiple Countries	11,476	-	-	Prevalent HD	Assess International variation in health literacy and association with mortality	Cohort	International sample from the DOPPS4 and DOPPS5 cohorts- randomly selected patients from dialysis units in participating countries [β]	-		BHLS (0-12)	Mortality	25
Eneanya [254] 2015 USA	152	[68]	60	Non-dialysis CKD 4-5	Investigate health literacy as a mediator of racial disparities in CPR knowledge	Cross-sectional	Adults at a single centre	56% white 44% black	<45, Non-English-speaking, Ethnicity other than black or white, Listed for transplant, Dementia	REALM	CPR Knowledge	34 (black 62%; white 14%)
Jang [202] 2014 USA	110	>65 (exact figure not known)	58	Prevalent HD	Compare medication label understanding to REALM-SF	Cross-sectional	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	23

Appendices

Study Year Location	n	Median age (years) [mean]	Male (%)	CKD stage	Aim	Design	Setting & recruitment method	Participants	Exclusion criteria	Health literacy measure	Outcome variables tested	Limited health literacy prevalence (%)
Marshall [255] 2015 NZ	99[α]	[56]	63	Prevalent dialysis (PD and HD)	Validate BHLS in multi-ethnic NZ population	Cohort (baseline data)	Random sample from single dialysis centre, stratified to include equal groups by ethnicity (NZ Māori/Pacific Peoples/Other) and dialysis location (home/centre)	35% NZ Māori; 35% Pacific Peoples; 30% white or other	<17. Logistic or safety risk to interviewers, severe mental illness, severe communication difficulty, unable to give informed consent	BHLS	-	42
Nelson [205] 2015 USA	208	[72]	56	Non-dialysis CKD3b-5	Relationship between health literacy, medicines management capacity and treatment adherence	Cross-sectional	Adults under regular nephrology care in a single unit		-	REALM	Medicines management capacity and self-reported medication adherence	23
Puher [207] 2014 USA	512	[66]	50	Non-dialysis CKD3-5	Assess relationship between health literacy and patient understanding	Cross-sectional	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	17
Singh [211] 2012 USA	101	-	49	Prevalent HD	Association of health literacy with dialysis quality measures	Cross-sectional	Adults in a single dialysis centre	-	None stated	STOFHLA	Laboratory values, infections, hospitalization, dialysis access	8
Singla [212] 2016 USA	74	[58]	57	Non-dialysis CKD 3-4	Identify prevalence and associations of low health literacy	Cohort	Participants already recruited to a clinical trial.	38% black; 8% white; 48% Hispanic	None stated	REALM	Demographics, hospitalization, dialysis initiation at 2 years	30
Weng 2 [256] 2014 USA	499	[54]	65	Non-dialysis CKD (n=203) and Prevalent dialysis (n=296)	RCT of an educational intervention to increase knowledge of living-donor kidney transplantation	Clinical trial (baseline data)	Single transplant centre.	Potential transplant candidates referred for evaluation	None stated	NVS	-	9 (Non-dialysis CKD 5%; Dialysis 11%)

Appendix C Additional material for ATTOM methods (Chapter 4)

C.1 ATTOM questionnaire

Access to Transplant and Transplant Outcome Measures
(ATTOM study)
Socio-demographic questionnaire

This questionnaire asks about you and your household.

Please answer each question by putting a 'R' in the box that applies, or entering details in the spaces provided

1. Is English your first Yes No language?

If 'No', please answer 1a and 1b below
1a What is your first language? …………………………….

1b Please tick one box below to show your fluency in English

Very basic / no fluency
Moderately fluent
Very fluent

2. How often do you need someone's help to read instructions, leaflets, or other written material from your doctor or pharmacy?

Never
Rarely
Sometimes
Often
Always

3. Were you born in the UK? No Yes

If 'No' how long have you lived in the UK………..years

4. Which one of the following ethnic groups best describes the one you belong to? Please choose ONE section from A to E, then tick the appropriate box to indicate your ethnic group.

A : White

British
Irish
Any other white background (please state………………………….)

B : Mixed

White and Black Caribbean
White and Black African
White and Asian
Any other mixed background (please state ……………………….)

C : Asian or Asian British

Indian
Pakistani
Bangladeshi
Any other Asian background (please state………………………….)

D : Black or Black British

Caribbean
African
Any other Black background (please state ………………………….)

E : Chinese or other ethnic group

Chinese
Any other (please state…………………….)

5. In the last 4 weeks which of the following best describes your employment status?

Working full-time
Working part-time
Unemployed
Student (includes pupil at school, those in training)
Looking after family home
Long-term sick or disabled
Retired from paid work
Not in paid work for some other reason (please state……………………..)

6. If you are not currently working have you been actively looking for work in the last 4 weeks?

☐ Yes ☐ No

7. Which of these qualifications do you have?

O/GCSE/CSE/School Certificate level
A level /Higher School Certificate
First degree (eg BA, BSc)

Higher degree (eg MSc, PhD, PGCE)
NVQ 1-03
NVQ 4-5
Other qualifications (e.g: City and Guilds) (please state……………………..) No qualification

8. Do you, or any members of your household, at present own or have continuous use of any motor vehicles (car, light van, including company vehicles if available for private use)?

☐ Yes ☐ No

If 'Yes', how many motor vehicles
1
2
3
4 or more

9. Which of the following best describes the accommodation you live in?

Owned by you (outright or with a mortgage)
Part rent, part owned (shared ownership)
Rented privately from council/housing association
Other (please specify..)

10. Which of the following best describes your marital status?

Single – never married
Married
Separated (but still legally married)
Divorced Widowed

11.

How many adults (age >18 years) live in your household including you? ☐

How many children (age <18 years) live in your household? ☐

12. Do you currently smoke cigarettes, cigar or a pipe? , ☐ No cigar,Yes

☐

If yes and you smoke cigarettes, approximately how many cigarettes do you smoke per day ☐

If ‘No’ are you an ex-smoker? No Yes

If you are an ex-smoker - how long ago did you stop smoking?
☐ years ☐ months

Appendix D Additional material for ATTOM baseline analysis (Chapter 5)

D.1 Effect of language on ethnicity-related differences in health literacy

Adding adjustment for English fluency to each model was found to reduce the effect of Ethnicity on the likelihood of limited health literacy to non-significance. This is shown in Table D.1.1.

D.1.1 The effect of adding adjustment for English fluency on the odds of limited health literacy in patients of Asian ethnicity

	Incident Dialysis OR (95% CI)	Wait-listed OR (95% CI)	Incident Transplant OR (95% CI)
Unadjusted	3.81 (2.90, 5.00)	3.01 (2.24, 4.29)	3.34 (2.35, 4.76)
After adjustment for English Fluency	1.32 (0.86, 2.03)	0.80 (0.46, 1.39	0.91 (0.51, 1.61)

D.2 Multiple imputation of missing data

Because of concern about the potential for non-response bias arising from exclusion of patients without complete data, most of whom had an incomplete record because of non-response to questions relating to socioeconomic status and the SILS, the proportions of missing data for key variables in each group are shown in Table D.2.1. Demographics and comorbidities of patients with complete and incomplete records were compared (Table D.2.2). Patients with incomplete records were significantly older and more likely to be Asian or diabetic. There were other differences in individual comorbidities. The missing data were therefore deemed to be 'Missing at Random' (MAR).[257]

D.2.1 Proportion of missing data for each variable by patient group

	Missing values by group (%)		
	Incident Dialysis n=2621	Wait-listed n=1959	Matched Controls n=2262
Single-Item Literacy Screener	158 (6.0)	211 (9.3)	100 (5.1)
Sex	0	0	0
Ethnicity	10 (0.4)	9 (0.4)	6 (0.3)
Language	157 (6.0)	206 (9.1)	97(5.0)
Comorbidities (examples)			
Heart Failure	33 (1.3)	10 (0.4)	28 (1.4)
Diabetes	25 (1)	7 (0.3)	25 (1.3)
Respiratory disease	33 (1.3)	10 (0.4)	27 (1.4)
Cirrhotic liver disease	35 (1.3)	13 (0.6)	27 (1.4)
Smoking	68 (2.6)	65 (2.9)	50 (2.6)
Qualifications	166 (6.3)	214 (9.5)	106 (5.4)
Car Ownership	162 (6.2)	208 (9.2)	99 (5.0)
Home ownership	166 (6.3)	211 (9.3)	100 (5.1)
Marital Status	170 (6.5)	213 (9.4)	104 (5.3)
Employment	165 (6.3)	211 (9.3)	103 (5.3)
Number of Children	167 (6.4)	210 (9.3)	102 (5.2)

D.2.2 Comparison of demographics and comorbidity between patients with complete data and those with missing data

	Complete cases n=6217(91%)	Incomplete cases n=625(9%)	p
Median age[IQR]	53[43-63]	52[41-62]	0.049
Male	3858(62)	399(64)	0.380
Ethnicity:			
White	4986(80)	440(73)	0.001
Asian	657(11)	91(15)	
Black	484(8)	54(9)	
Chinese	44(0.7)	9(1.5)	
Mixed-race	46(0.7)	1(6)	
Modified Charlson index			
0	3598(58)	370(59)	0.197
1-2	1900(31)	200(32)	
3-4	495(8)	40(6)	
>_5	224(4)	15(2)	
Diagnoses included in modified Charlson index:			
Myocardial infarction	381(6)	24(4)	0.021
Heart failure	239(4)	21(3)	0.915
Peripheral vascular disease	343(6)	33(5)	0.728
Cerebrovascular disease	393(6)	34(6)	0.819
Dementia	8(0.13)	2(0.36)	0.177
Respiratory disease	526(8)	33(6)	0.036
Diabetes	1652(27)	192(34)	<0.001
Diabetic nephropathy	1105(18)	140(25)	<0.001
Cirrhotic liver disease	40(1)	6(1)	0.235
Leukaemia	10(0.16)	2(0.32)	0.365
Lymphoma	99(2)	3(0.5)	0.029

To investigate the effect of these missing data on the results of logistic regression models, data were imputed for each group of patients (Incident Dialysis/Wait-listed/Incident Transplant). Imputation by chained equations (ICE) was performed using Stata 12 (StataCorp LP, College station, TX, USA). For each group, 20 imputed datasets were generated. Variables used in the imputation models included all variables considered for inclusion in multivariate models (SILS score, age, sex, ethnicity, individual comorbidities, smoking, qualifications, employment, accommodation, car ownership, marital status, number of children and birth in the UK). Rate of Limited health literacy and modified Charlson indices were then recalculated using the imputed comorbidities and SILS scores.

Regression models were re-fitted using the same backwards-stepwise approach as described in the *Methods* section. Pooled estimates of logistic regression models from all 20 imputed datasets were compared to the original models (Table D.2.3).No additional dependent variables reached statistical significance in any group, so the final regression models for the imputed data included no new variables. The patterns observed in regression models from imputed data were largely similar to those using complete cases only. In all groups, patients who achieved ‘other’ qualifications (mostly vocational qualifications) were significantly less likely to have limited health literacy (OR 0.34). In the wait-listed group, there were some changes in the effect of comorbidity and employment status on the likelihood of limited health literacy- including loss of significance for ‘current’ smoking status.

D.2.3 Comparison of regression models using imputed data and models using data from complete cases only

Bold type indicates statistical significance.

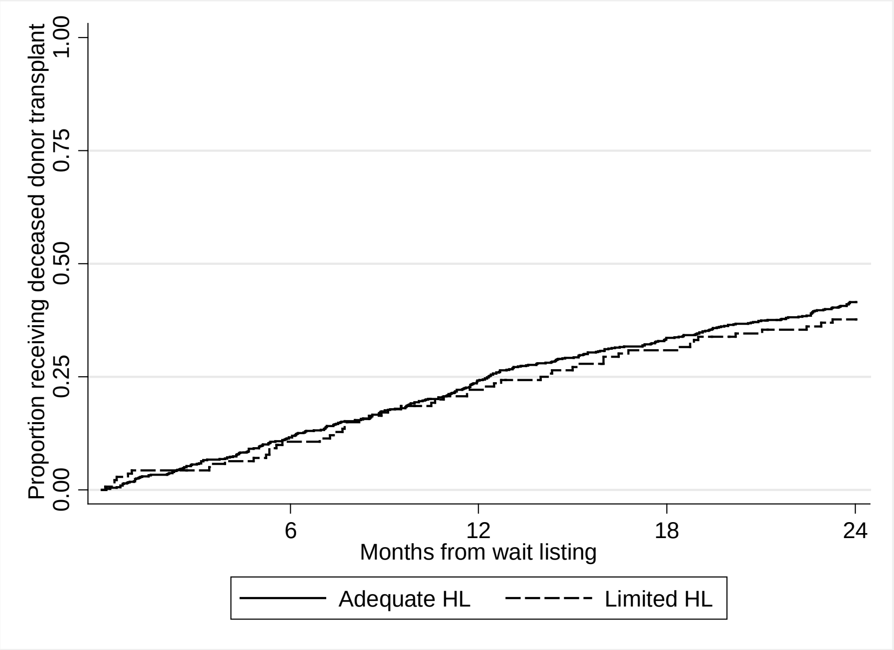
	Incident Dialysis		Wait-Listed		Incident Transplant	
	Complete records only	Pooled Imputed data	Complete records only	Pooled imputed data	Complete records only	Pooled imputed data
	n=2399	n=2621	n=1785	n=1959	n=2030	n=2262
Age	**0.98 (0.97-0.99)**	**0.98 (0.97-1)**	**0.97 (0.96-0.99)**	**0.98 (0.96-0.99)**	0.98 (0.97-1)	0.99 (0.97-1)
Male sex	1.04 (0.81-1.34)	1.04 (0.81-1.34)	1.18 (0.85-1.63)	1.18 (0.85-1.64)	1.08 (0.77-1.51)	1.07 (0.77-1.5)
Ethnicity (Ref: White)						
Asian	1.39 (0.83-2.31)	1.52 (0.91-2.52)	0.8 (0.43-1.5)	0.84 (0.46-1.54)	0.99 (0.52-1.89)	1 (0.5-1.99)
Black	1.15 (0.72-1.83)	1.13 (0.71-1.8)	0.55 (0.29-1.02)	0.63 (0.35-1.14)	**0.21 (0.08-0.56)**	**0.23 (0.09-0.59)**
Chinese	0.32 (0.07-1.56)	0.46 (0.11-1.93)	0.45 (0.09-2.34)	0.53 (0.11-2.5)	1.54 (0.35-6.74)	1.27 (0.29-5.58)
Mixed-race	0.93 (0.2-4.23)	1.08 (0.26-4.49)	0.58 (0.1-3.41)	0.54 (0.1-3.07)	0.47 (0.09-2.55)	0.53 (0.1-2.88)
English Fluency (Ref: English 1st Language)						
Good	1.11 (0.61-2.01)	1.07 (0.59-1.96)	1.38 (0.68-2.79)	1.21 (0.61-2.38)	1.33 (0.59-3.03)	1.21 (0.53-2.75)
Moderate	**6.19 (3.54-10.82)**	**5.71 (3.27-9.96)**	**7.84 (4.1-15)**	**7.36 (3.9-13.88)**	**7.38 (3.55-15.35)**	**7.3 (3.43-15.53)**
Poor or no English	**26.54 (12.08-58.3)**	**19.25 (9.13-40.61)**	**44.31 (16.33-120.23)**	**50.2 (18.89-133.4)**	**32.31 (13.62-76.64)**	**35.79 (14.79-86.57)**
Modified Charlson Index (Ref: 0)						
1-2	**2.52 (1.88-3.38)**	**2.37 (1.78-3.16)**	**1.87 (1.32-2.63)**	**1.59 (1.13-2.23)**	**2.28 (1.63-3.19)**	**2.11 (1.5-2.95)**
3-4	**2.65 (1.82-3.84)**	**2.51 (1.73-3.64)**	1.76 (0.89-3.5)	1.49 (0.77-2.9)	**2.32 (1.25-4.31)**	**2.06 (1.13-3.77)**
>4	**2.31 (1.44-3.72)**	**2.31 (1.45-3.68)**	**2.91 (1.03-8.23)**	2.37 (0.85-6.61)	0.42 (0.05-3.72)	0.55 (0.07-4.41)
Depression	**1.61 (1.08-2.4)**	**1.62 (1.09-2.39)**				
Psychosis	**7.69 (2.1-28.17)**	**7.11 (2.01-25.11)**	**7.57 (1.42-40.41)**	**6.93 (1.36-35.43)**	**7.92 (1.12-55.93)**	**7.43 (1.09-50.72)**
Smoking status (ref: Never)						
Current Smoker	**0.68 (0.48-0.96)**	**0.69 (0.49-0.96)**	**0.6 (0.37-0.95)**	0.64 (0.4-1.01)		
Ex-smoker	0.87 (0.66-1.14)	0.85 (0.65-1.12)	1.23 (0.84-1.8)	1.21 (0.83-1.77)		

	Incident Dialysis		Wait-Listed		Incident Transplant	
	Complete records only	Pooled Imputed data	Complete records only	Pooled imputed data	Complete records only	Pooled imputed data
	n=2399	n=2621	n=1785	n=1959	n=2030	n=2262
Highest educational level (Ref: None)						
High School level	**0.43 (0.32-0.56)**	**0.55 (0.41-0.73)**	**0.35 (0.25-0.51)**	**0.43 (0.3-0.62)**	**0.42 (0.29-0.6)**	**0.45 (0.31-0.65)**
University Level	**0.24 (0.16-0.38)**	**0.25 (0.16-0.4)**	**0.23 (0.13-0.41)**	**0.21 (0.11-0.38)**	**0.13 (0.07-0.25)**	**0.12 (0.06-0.25)**
Other qualification	0.69 (0.46-1.04)	**0.34 (0.22-0.54)**	0.69 (0.38-1.26)	**0.37 (0.22-0.63)**	0.95 (0.55-1.64)	**0.4 (0.24-0.65)**
Employment (Ref: Full time)						
Part time	1.46 (0.65-3.29)	1.45 (0.64-3.29)	**3.23 (1.51-6.88)**	**2.81 (1.35-5.84)**	1.62 (0.77-3.41)	1.67 (0.8-3.5)
Unemployed	**2.47 (1.19-5.11)**	**2.21 (1.06-4.63)**	**3.75 (1.76-8)**	**3.32 (1.59-6.91)**	**2.19 (1.09-4.42)**	**2.37 (1.2-4.69)**
Student	1.09 (0.13-9.26)	0.91 (0.12-7.14)			1.51 (0.32-7.15)	1.67 (0.36-7.71)
Retired	**3.94 (2.05-7.57)**	**3.44 (1.79-6.59)**	**2.97 (1.4-6.32)**	**2.53 (1.24-5.17)**	**2.26 (1.17-4.38)**	**2.26 (1.17-4.38)**
Not working(other)	2.84 (0.79-10.25)	2.44 (0.68-8.8)	**9.73 (3.07-30.86)**	2.72 (0.92-8.07)	1.83 (0.6-5.58)	2.01 (0.67-6.02)
Looking after home	1.67 (0.57-4.89)	1.75 (0.62-4.93)	**3.63 (1.17-11.25)**	3.08 (0.99-9.56)	**4.76 (1.96-11.57)**	**5.16 (2.1-12.68)**
Long term sick/disability	**4.99 (2.71-9.2)**	**4.52 (2.46-8.29)**	**6.82 (3.62-12.86)**	**6.24 (3.43-11.38)**	**3.99 (2.36-6.75)**	**4.2 (2.51-7.02)**
Car owner	**0.61 (0.47-0.79)**	**0.61 (0.47-0.8)**	**0.6 (0.42-0.85)**	**0.63 (0.44-0.89)**	**0.58 (0.40-0.83)**	**0.58 (0.40-0.84)**
Home owner	**0.69 (0.53-0.9)**	**0.68 (0.52-0.88)**				
Number of Children (Ref: None)						
1-2	1.09 (0.78-1.53)	1.08 (0.76-1.52)				
>2	**2.50 (1.30-4.82)**	**2.50 (1.30-4.82)**				

Appendix E Additional material for ATTOM prospective analysis (Chapter 6)

E.1 Incident dialysis group, sensitivity analysis

E.1.1 Time from deceased-donor transplant wait-listing to deceased-donor transplantation, censored at 2 years, at death or at removal from the transplant list (including after living-donor transplant), whichever was earlier.



Chance of transplantation	Unadjusted HR (95% CI)	0.89 (0.67,1.20)
n=877	p	0.5

E.1.2 Access to deceased-donor transplant wait-listing and living-donor transplantation, excluding patients previously transplanted (n=298)

		Model			
		1 Unadjusted	2 + Age/Sex	3 +Ethnicity/Language	4 +PRD/Comorbidity
Pre-emptively wait-listed	OR	0.68	0.67	0.75	0.89
	(95% CI)	(0.47,0.97)	(0.47,0.96)	(0.51,1.09)	(0.60,1.33)
n=2039	p	**0.031**	**0.031**	0.1	0.6
Chance of transplant wait-listing	HR	0.72	0.72	0.64	0.69
	(95% CI)	(0.58,0.91)	(0.57,0.90)	(0.50,0.82)	(0.53,0.89)
n=1781	p	**0.005**	**0.004**	**<0.001**	**0.004**
Chance of transplantation (any donor type)	HR	0.53	0.54	0.55	0.62
	(95% CI)	(0.38,0.73)	(0.39,0.75)	(0.39,0.78)	(0.44,0.88)
n=2110	p	**<0.001**	**<0.001**	**0.001**	**0.008**
Chance of living-donor transplantation	HR	0.35	0.37	0.33	0.39
	(95% CI)	(0.20,0.62)	(0.21,0.65)	(0.18,0.60)	(0.21,0.73)
n=2113	p	**<0.001**	**0.001**	**<0.001**	**0.003**

E.2 Missing data

Table E.2.1 shows the proportion of missing data for each outcome variable. Between 0 and 34% of data were missing for the outcome variables tested.

E.2.1 Proportion of missing values for outcome variables

Incident dialysis cohort, n=2621	Number with missing data	Total n for variable	% of total
Response to SILS	158	2621	6
Late presentation	315	2621	12
Initial dialysis modality	10	2621	0.4
Dialysis access (if HD was initial dialysis modality)	24	2621	0.9
Unless dead or transplanted at 15 months:			
Hb	286	2304	12
Calcium	249	2307	11
Phosphate	246	2308	11
iPTH (excluding Scotland)	419	2059	20
URR (excluding peritoneal dialysis or haemodialysis <3x/week)	528	1562	34
Systolic BP (excluding peritoneal dialysis)	412	1609	26
PD failure (of those whose first dialysis modality is PD)	34	484	7
Transplant wait-listing (excluding previously transplanted)	1	2216	<0.1
Transplantation (excluding previously transplanted)	1	2279	<0.1
Living-donor transplantation (excluding previously transplanted)	1	2282	<0.1
Survival	1	2215	<0.1
Incident transplant cohort, n=2262			
Response to SILS	211	2262	9
3 month eGFR (if alive)	364	2232	16
12 month eGFR (if alive)	280	2181	13
24 month eGFR (if alive)	378	2041	19

The lowest proportion of missing outcome data were for the time-to-event variables in the incident dialysis group. However, multivariate analysis for these outcomes could also be affected by missing health literacy, demographic or comorbidity data. The multivariate models for transplant wait-listing, transplantation and living-donor transplantation omitted 7-11% of subjects because of missing data. To test the hypothesis that subjects omitted from this model were significantly different in terms of outcome compared to those included, univariate survival models were fitted comparing subjects included vs excluded from these models. These (Table E.2.2) showed no significant differences.

E.2.2 Time to deceased-donor transplant wait-listing, transplantation or living-donor transplant for subjects excluded from multivariate models vs those included

Unadjusted hazard of event for those with incomplete records who were excluded from multivariate models (compared to those with complete records)		
Chance of transplant wait-listing	HR (95% CI)	1.09 (0.80,1.49)
n=2281	p	0.6
Chance of transplantation (any donor type)	HR (95% CI)	1.17 (0.82,1.70)
n=2278	p	0.4
Chance of living-donor transplantation	HR (95% CI)	1.02 (0.57,1.84)
n=2281	p	0.9

Other variables including late presentation, laboratory and clinical data imported from the UK Renal Registry and NHSBT had a higher proportion of missing data (11-34%), often because of non-return of such data from individual renal centres. Table E.2.3 compares the characteristics of patients with complete records (included in the reported multivariate models) with patients with incomplete records (excluded from multivariate models) for three example outcome analyses. It should be noted that this comparison relies on completeness of other variables in those with missing data for a single variable. For instance, a patient with missing data on transplant wait-listing may also be more likely to have a missing health literacy variable. Accepting this limitation, there were significant differences in health literacy, demographics and morbidity between those with complete vs incomplete records.

E.2.3 Characteristics of patients with missing data for haemoglobin, time to transplant wait-listing (Incident Dialysis group) and for 12-month eGFR (Incident Transplant group). Shown as frequency (%) unless otherwise stated

	Incident Dialysis group						Incident transplant group		
	Hb			Late presentation			12 month eGFR		
	Complete records (n=1664)	Incomplete records (n=640)	p	Complete records (n=2154)	Incomplete records (n=467)		Complete records (n=1730)	Incomplete records (n=451)	p
Limited HL	302 (18)	126 (25)	**0.001**	404 (19)	77 (25)	**0.011**	193 (11)	50 (20)	**<0.001**
Median age [IQR]	58 [47,67]	57 [46.5,65]	0.2	58 [47,67]	57 [46,65]	0.2	50 [40,59]	48 [38,59]	0.07
Male	1083 (65)	419 (65)	0.8	1400 (65)	301 (64)	0.8	1082 (63)	282 (63)	0.9
Ethnicity:									
White	1368 (82)	456 (72)	**<0.001**	1773 (82)	324 (71)	**<0.001**	1436 (83)	365 (83)	0.5
Asian	165 (10)	102 (16)		210 (10)	84 (18)		166 (10)	41 (9)	
Black	115 (7)	62 (10)		144 (7)	41 (9)		98 (6)	32 (7)	
Chinese	9 (1)	7 (1)		15 (1)	3 (1)		14 (1)	2 (0.5)	
Mixed-race	7 (0.4)	5 (1)		12 (1)	5 (1)		16 (1)	2 (0.5)	
English first language	1466 (88)	412 (81)	**0.001**	1893 (89)	246 (80)	**<0.001**	1521 (88)	235 (93)	0.1
Other first language, English Fluency:									
Good	86 (5)	35 (7)		114 (5)	21 (7)		99 (6)	9 (4)	
Moderate	65 (4)	38 (8)		87 (4)	25 (8)		64 (4)	4 (2)	
Poor	47 (3)	22 (4)		60 (3)	17 (6)		46 (3)	6 (2)	
Modified Charlson index									
0	696 (42)	270 (42)	0.3	899 (42)	198 (42)	0.3	1293 (75)	204 (45)	**<0.001**
1-2	630 (38)	260 (41)		805 (37)	188 (40)		352 (20)	208 (46)	
3-4	221 (13)	76 (12)		292 (14)	55 (12)		68 (4)	34 (8)	
>_5	117 (7)	34 (5)		158 (7)	26 (6)		17 (1)	5 (1)	
Primary Renal Disease									
Diabetes	438 (26)	176 (29)	0.09	546 (25)	145 (33)	**0.005**	140 (8)	167 (38)	**<0.001**
Glomerulonephritis	260 (16)	88 (14)		336 (16)	60 (14)		440 (25)	75 (17)	
Pyelonephritis	102 (6)	33 (5)		131 (6)	26 (6)		203 (12)	26 (6)	
Hypertension	114 (7)	31 (5)		139 (6)	19 (4)		95 (5)	20 (5)	
Polycystic Kidney Disease	133 (8)	46 (8)		174 (8)	33 (8)		282 (16)	38 (9)	
Renovascular Disease	53 (3)	16 (3)		74 (3)	11 (3)		24 (1)	8 (2)	
Other	311 (19)	144 (24)		432 (20)	95 (22)		368 (21)	66 (15)	
Uncertain	253 (15)	76 (12)					178 (10)	39 (9)	

E.3 Mediation- sensitivity analysis- Car ownership as additional covariate

E.3.1 Analysis of health literacy as a mediator of the effect of low educational level (no educational qualifications) on time to deceased-donor transplant wait-listing.

Car ownership as additional covariate.

Time to transplant wait-listing, n=2016	Path/effect	Estimate (95% CI)	Time-to-event ratio (95% CI)	p
Linear Regression				
	a no qualifications->lower health literacy	0.47 (0.36,0.58)	**-**	**<0.001**
Weibull model 1				
	c no qualifications->wait-listing (model excludes health literacy)	0.16 (-0.03,0.35)	1.17 (0.97,1.42)	0.09
Weibull model 2				
	b’ health literacy->wait-listing	0.14 (0.06,0.21)	1.15 (1.06,1.24)	**0.001**
	c’ no qualifications->wait-listing (model includes health literacy)	0.09 (-0.10,0.28)	1.09 (0.90,1.32)	0.4
Calculate direct/indirect effects				
	Indirect effect (ab’)	0.06 (0.02,0.10)	1.07 (1.02,1.11)	**0.001**
	Total effect (by c’ +ab’)	0.15 (-0.04,0.34)	1.16 (0.96,1.40)	0.1
	Proportion mediated	**Not calculated: no significant total effect**		

E.3.2 Analysis of health literacy as a mediator of the effect of low educational level (no educational qualifications) on time to living-donor transplant.

Car ownership as additional covariate.

Time to living-donor transplant, n=2391	**Path/effect**	**Estimate (95% CI)**	**Time-to-event ratio (95% CI)**	**p**
Linear Regression				
	a no qualifications-> lower health literacy	0.47 (0.37,0.57)	**-**	**<0.001**
Weibull model 1				
	c no qualifications->transplantation (model excludes health literacy)	0.23 (0.04,0.43)	1.26 (1.04,1.54)	**0.020**
Weibull model 2				
	b’ health literacy-> transplantation	0.12 (0.03,0.21)	1.12 (1.04,1.23)	**0.006**
	c’ no qualifications-> transplantation (model includes health literacy)	0.18 (-0.02,0.38)	1.20 (0.98,1.46)	0.08
Calculate direct/indirect effects				
	Indirect effect (ab’)	0.06 (0.01,0.10)	1.06 (1.01,1.11)	**0.008**
	Total effect (by c’ +ab’)	0.24 (0.04,0.44)	1.27 (1.04,1.55)	**0.019**
	Proportion mediated		**24%**	

E.3.3 Analysis of health literacy as a mediator of the effect of low educational level (no educational qualifications) on time to transplant from any donor type.

Car ownership as additional covariate

Time to transplantation n=2388	**Path/effect**	**Estimate (95% CI)**	**Time-to-event ratio (95% CI)**	**p**
Linear Regression				
	a no qualifications->lower health literacy	0.48 (0.37,0.58)	-	**<0.001**
Weibull model 1				
	c no qualifications-> transplantation (model excludes health literacy)	0.27 (-0.06,0.61)	1.32 (0.94,1.85)	0.1
Weibull model 2				
	b’ health literacy-> transplantation	0.20 (0.03,0.36)	1.22 (1.03,1.43)	**0.018**
	c’ no qualifications-> transplantation (model includes health literacy)	0.19 (-0.15,0.53)	1.21 (0.86,1.71)	0.3
Calculate direct/indirect effects				
	Indirect effect (ab’)	0.09 (0.01,0.17)	1.10 (1.01,1.19)	**0.022**
	Total effect (by c’ +ab’)	0.29 (-0.05,0.63)	1.33 (0.95,1.87)	0.1
	Proportion mediated	**Not calculated: no significant total effect**		

E.4 Mediation - sensitivity analysis- white patients only

E.4.1 Sensitivity analysis (white patients only) of health literacy as a mediator of the effect of low educational level (no educational qualifications) on time to transplant wait-listing

Time to transplant wait-listing, n=1626	**Path/effect**	**Estimate (95% CI)**	**Time-to-event ratio (95% CI)**	**p**
Linear Regression				
	a no qualifications-> lower health literacy	0.37 (0.25,0.49)	-	**<0.001**
	Weibull model 1			
	c no qualifications->wait-listing (model excludes health literacy)	0.20 (-0.03,0.42)	1.21 (0.97,1.52)	0.09
	Weibull model 2			
	b’ health literacy->wait-listing	0.16 (0.05,0.27)	1.17 (1.05,1.31)	**0.003**
	c’ no qualifications->wait-listing (model includes health literacy)	0.14 (-0.09,0.36)	1.15 (0.91,1.44)	0.2
	Calculate direct/indirect effects			
	Indirect effect (ab’)	0.06 (0.02,0.10)	1.06 (1.02,1.11)	**0.008**
	Total effect (by c’ +ab’)	0.20 (-0.03,0.42)	1.22 (0.97,1.52)	0.09
	Proportion mediated	**Not calculated: no significant total effect**		

E.4.2 Sensitivity analysis (white patients only) of health literacy as a mediator of the effect of low educational level (no educational qualifications) on time to living-donor transplant

Time to living-donor transplant, n=1935	**Path/effect**	**Estimate (95% CI)**	**Time-to-event ratio (95% CI)**	**p**
Linear Regression				
	a no qualifications-> lower health literacy	0.39 (0.29,0.50)	**-**	**<0.001**
Weibull model 1				
	c no qualifications-> transplantation (model excludes health literacy)	0.40 (0.01,0.78)	1.48 (1.01,2.19)	**0.042**
Weibull model 2				
	b' health literacy-> transplantation	0.31 (0.08,0.53)	1.36 (1.09,1.70)	**0.007**
	c' no qualifications-> transplantation (model includes health literacy)	0.30 (-0.09,0.69)	1.35 (0.92,1.98)	0.1
Calculate direct/indirect effects				
	Indirect effect (ab')	0.12 (0.03,0.21)	1.13 (1.03,1.24)	**0.011**
	Total effect (by c' +ab')	0.42 (0.03,0.81)	1.52 (1.03,2.24)	**0.034**
	Proportion mediated		**29%**	

E.4.3 Sensitivity analysis (white patients only) of health literacy as a mediator of the effect of low educational level (no educational qualifications) on time to transplant from any donor type

Time to transplantation n=1933	**Path/effect**	**Estimate (95% CI)**	**Time-to-event ratio (95% CI)**	**p**
Linear Regression				
	a no qualifications-> lower health literacy	0.39 (0.28,0.50)	-	**<0.001**
Weibull model 1				
	c no qualifications-> transplantation (model excludes health literacy)	0.31 (0.09,0.54)	1.36 (1.09,1.71)	**0.007**
Weibull model 2				
	b' health literacy-> transplantation	0.13 (0.02,0.23)	1.14 (1.02,1.26)	**0.019**
	c' no qualifications-> transplantation (model includes health literacy)	0.26 (0.04,0.49)	1.30 (1.04,1.64)	**0.024**
Calculate direct/indirect effects				
	Indirect effect (ab')	0.05 (0.01,0.09)	1.05 (1.01,1.10)	**0.026**
	Total effect (by c' +ab')	0.31 (0.09,0.54)	1.37 (1.09,1.72)	**0.007**
	Proportion mediated		**16%**	

Appendix F Published results

The following pages contain copies of published papers arising from work included in this thesis, the citations for which are as follows.

- **Taylor, D. M., S. D. S. Fraser, J. A. Bradley, C. Bradley, H. Draper, W. Metcalfe, G. C. Oniscu, C. R. V. Tomson, R. Ravanan and P. J. Roderick (2017). "A Systematic Review of the Prevalence and Associations of Limited Health Literacy in CKD." Clin J Am Soc Nephrol.**
- **Taylor DM, Fraser SD, Oniscu GC, Tomson C, Ravanan R, Roderick PJ. Health literacy and patient outcomes in chronic kidney disease: a systematic review Nephrology Dialysis Transplantation 2017: gfx293-gfx293.**
- **Taylor, D. M., J. A. Bradley, C. Bradley, H. Draper, R. Johnson, W. Metcalfe, G. Oniscu, M. Robb, C. Tomson, C. Watson, R. Ravanan and P. Roderick (2016). "Limited health literacy in advanced kidney disease." Kidney International 90(3): 685-695.**

CJASN ePress. Published on May 9, 2017 as doi: 10.2215/CJN.12921216

Article

A Systematic Review of the Prevalence and Associations of Limited Health Literacy in CKD

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Abstract

Background and objectives The self-management and decision-making skills required to manage CKD successfully may be diminished in those with low health literacy. A 2012 review identified five papers reporting the prevalence of limited health literacy in CKD, largely from United States dialysis populations. The literature has expanded considerably since.

Design, setting, participants, & measurements We used systematic review, pooled prevalence analysis, metaregression, and exploration of heterogeneity in studies of patients with CKD (all stages).

Results From 433 studies, 15 new studies met the inclusion criteria and were analyzed together with five studies from the 2012 review. These included 13 cross-sectional surveys, five cohort studies (using baseline data), and two using baseline clinical trial data. Most (19 of 20) were from the United States. In total, 12,324 patients were studied (3529 nondialysis CKD, 5289 dialysis, 2560 transplant, and 946 with unspecified CKD; median =198.5; IQR, 128.5–260 per study). Median prevalence of limited health literacy within studies was 23% (IQR, 16%–33%), and pooled prevalence was 25% (95% confidence interval, 20% to 30%) with significant between-study heterogeneity (I^2=97%). Pooled prevalence of limited health literacy was 25% (95% confidence interval, 16% to 33%; I^2=97%) among patients with CKD not on dialysis, 27% (95% confidence interval, 19% to 35%; I^2=96%) among patients on dialysis, and 14% (95% confidence interval, 7% to 21%; I^2=97%) among patients with transplants. A higher proportion of nonwhite participants was associated with increased limited health literacy prevalence (P=0.04), but participant age was not (P=0.40). Within studies, nonwhite ethnicity and low socioeconomic status were consistently and independently associated with limited health literacy. Studies were of low or moderate quality. Within-study participant selection criteria had potential to introduce bias.

Conclusions Limited health literacy is common in CKD, especially among individuals with low socioeconomic status and nonwhite ethnicity. This has implications for the design of self-management and decision-making initiatives to promote equity of care and improve quality. Lower prevalence among patients with transplants may reflect selection of patients with higher health literacy for transplantation either because of less comorbidity in this group or as a direct effect of health literacy on access to transplantation.

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Introduction

CKD affects 12% of United States adults and is associated with significant morbidity and mortality, predominantly through increased cardiovascular risk (1). CKD progression further increases cardiovascular risk (2) and the risk of requiring RRT (3). CKD management aims to reduce these risks and prepare people with advanced CKD for dialysis, transplantation, or conservative care (4). Increasingly, CKD management involves shared decision-making and self-care activities, which are actively promoted in health care policy (5,6). However, these activities require patients to learn, understand, appraise, and apply knowledge of a complex disease process and its treatment. As CKD progresses, the burden of self-management activities increases, whereas patients' capacity (7,8) to perform these activities may reduce because of disease-related reduction in function (9). Furthermore, CKD is associated with low socioeconomic status (SES) (10), and therefore, people with CKD may lack the social resources needed for successful CKD management (8). Effective self-management may, therefore, depend on individual skills in managing health, such as health literacy (11).

Health literacy is a personal attribute that "entails people's knowledge, motivation and competences to access, understand, appraise and apply health information" (12). As a potentially modifiable factor influencing individual health, it is the focus of an expanding field of research. Multiple tools have been developed to measure health literacy or screen for low or "limited" health literacy (13). In general populations, limited health literacy is associated with poorer health (14), less efficient use of health care services (15), and higher mortality (16). However, investigation of limited health literacy in CKD has been relatively limited: a 2012 systematic review identified four studies of patients on hemodialysis, one study of patients with transplants, and one including patients with early CKD (17). Only 1405 patients were studied in total. Limited health literacy was associated with lower SES (18–20) and increased comorbidity (19). One study showed increased mortality among patients on dialysis with limited health literacy (21). The review identified a need for studies measuring health literacy among patients with CKD stages 1–4 and studies from outside the United States.

Since this review, investigation of limited health literacy as a barrier to effective clinician-patient communication has been identified as a research priority in CKD (22). Health literacy measures specific to CKD have been developed and validated (23,24). A Cochrane review of health literacy–focused interventions in CKD is underway (25). We recognized that health literacy research in CKD had increased significantly. This study aimed to 1) re-explore the prevalence and sociodemographic associations of limited health literacy among patients with CKD, 2) compare the prevalence of limited health literacy between patients with nondialysis CKD, patients on dialysis, and patients with a kidney transplant, and 3) identify causes of heterogeneity in reported results.

Materials and Methods

The review protocol was registered with the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO; registration number D42016036742).

English language references from between December of 2010 and July of 2016 were identified from Medline, Embase, Ovidfulltext (including Psycharticles), Health Management Information Consortium, Cumulative Index to Nursing and Allied Health Literature, and Psychinfo. The search strategy (Supplemental Material, Supplemental Figure 1) was developed from the 2012 review, a Cochrane systematic review protocol for health literacy interventions in CKD (25), and review articles of health literacy measurement tools (23,26–31). In addition to database searches, reference lists from articles included in this review and from other review articles were hand searched.

Two reviewers (D.M.T. and S.F.) independently assessed journal articles for inclusion by three criteria. (*1*) At least 50 adults over 18 years old with CKD were included (aiming to identify studies with a predominantly quantitative rather than qualitative focus). (2) The study used a validated measure to quantitatively describe health literacy. (3) The study reported the prevalence of limited health literacy or data from which this could be derived.

Full texts of journal articles were reviewed if the first criterion and either of the other two were met. Authors were contacted if required to establish if a study should be included or request additional data. Articles that met the inclusion criteria were analyzed along with the five articles included in the 2012 review. In a sensitivity analysis, searches were widened to include unpublished studies available as abstracts from nephrology and health literacy conferences.

Study quality was scored independently by D.M.T. and S.F. guided by a review of tools for assessing the quality of observational studies (32). Studies were assigned scores for sample size, setting, recruitment methods, and potential for unrecognized confounding of results. Scores were combined to indicate study quality and used to inform grading of studies as low, moderate, or high quality. However, this scoring acted as a guide only, and grading of studies was decided by discussion between the two reviewers.

For each study, the prevalence of limited health literacy, number of unique participants, study methods, and demographics of participants were recorded. A meta-analysis was performed with subgroup analysis by CKD treatment stage (nondialysis CKD, dialysis, or transplant) and health literacy measure. Results were presented as Forest plots, with 95% confidence intervals (95% CIs) for each prevalence value and the pooled prevalence of limited health literacy. I^2 statistics were calculated to measure the degree of heterogeneity between studies and subgroups. A random effects model was used, because we expected to find significant heterogeneity in the prevalence of limited health literacy on the basis of the results of the 2012 review (9). Univariate metaregression was performed for continuous variables, which included the proportion of patients with nonwhite ethnicity and the age of participants (mean or median). If data on treatment stage, age, or ethnicity were unavailable, studies were excluded from each analysis.

For studies where more than one validated health literacy measure was used, scores from the Short Test of Functional Health Literacy in Adults (STOFHLA) are presented here because of its use as a reference measure to validate health literacy screening tools (23,24,33). Analyses were then repeated using scores from other measures to establish if this altered the overall results. Sociodemographic characteristics significantly associated with limited health literacy were summarized, with covariates included in multivariate models, to identify independent associations. Statistical significance within studies was defined by individual study methods. A P value of <0.05 was selected *a priori* to define statistical significance for meta-analysis and metaregression. Analyses were performed using the user-written commands metaprop and metareg in Stata 12 (StataCorp LP).

Results

Figure 1 shows the study selection process, which identified 433 unique studies, 15 of which met the inclusion criteria (23,24,34–46) with full agreement between the two reviewers. Table 1 summarizes the 15 new studies in addition to five studies included in the 2012 review (18–21,47). All 20 studies are included in the following description and analysis.

Of 20 studies, 13 were cross-sectional surveys, five used baseline data from cohort studies, and two used baseline data from clinical trials. One study presented United Kingdom data (44), and all others reported from the United States. Study quality was graded as low for 15 studies and moderate for five studies (18,21,42–44).

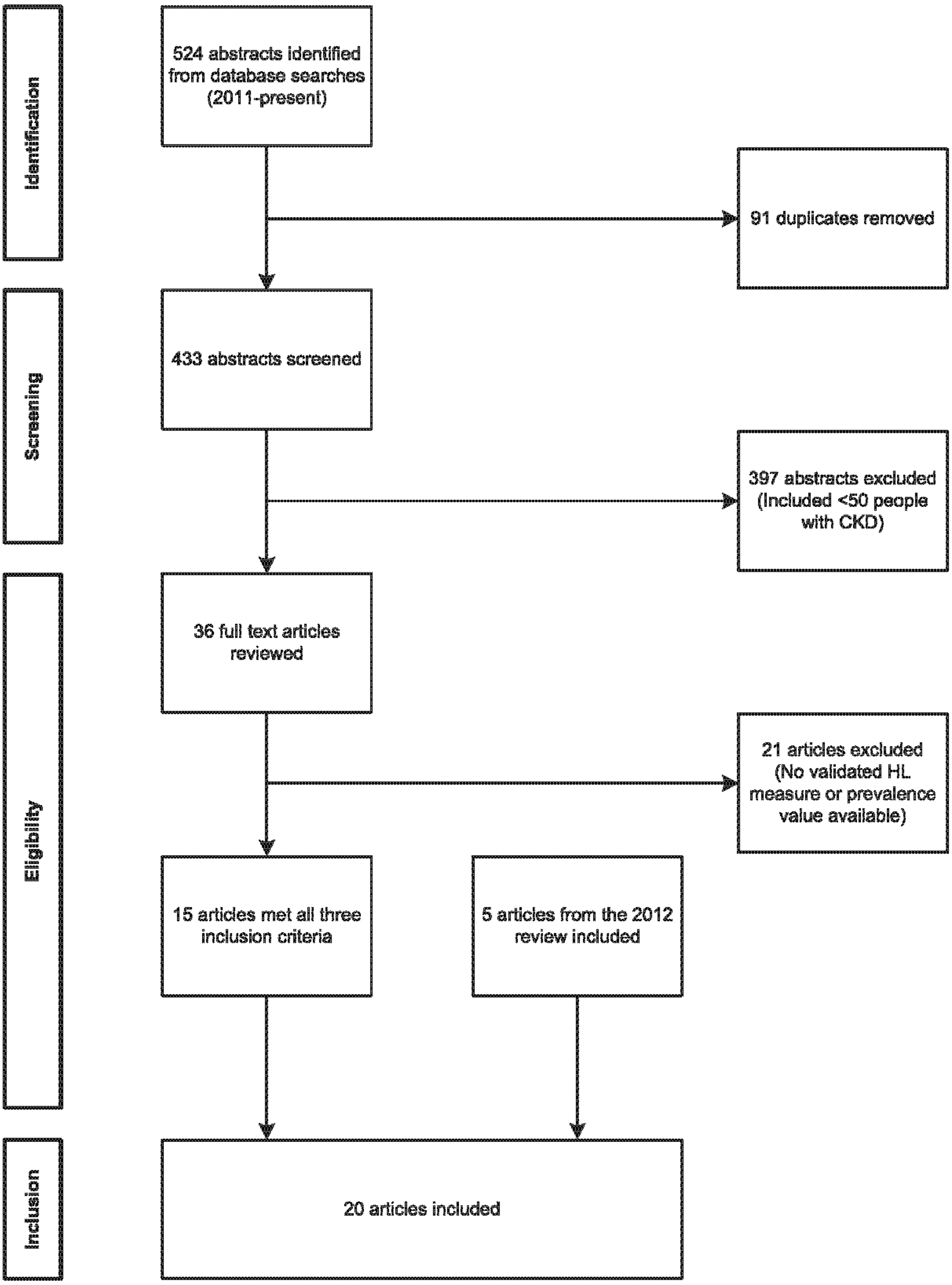


Figure 1. | **Study selection process.** HL, health literacy.

In total, 12,324 patients were studied, including 1327 patients included in the 2012 review. This included 3529 patients with nondialysis CKD from seven studies, 5289 patients on dialysis from ten studies, and 2560 patients with transplants from five studies. Five studies included patients from multiple treatment stages. The prevalence of limited health literacy by treatment stage was not available for 946 patients from two studies (40,41), even after communication

Table 1. Characteristics of studies included in the review

Study/ Reference/ Year/ Location/ *N*	Median Age, yr [Mean]	Men, %	CKD Stage	Aim	Design	Setting and Recruitment Method	Participants	Exclusion Criteria	Health Literacy Measure	Outcome Variables Tested	Prevalence of Limited Health Literacy, %
Adeseun (34) 2012 US 72	[52]	68	Incident dialysis (HD or PD)	Examine relationship between health literacy and CV disease risk factors	Cohort (baseline data)	Adults from transplant evaluation clinics taking part in the Dialysis Heart and Bone Study	100% with limited health literacy were black compared with 50% of those with adequate health literacy	Previous coronary revascularization, cardiac devices, or weight >350 lb	STOFHLA	BP, lipid profile, waist-to-hip ratio, BMI, tobacco use	21
Boulware (35) 2013 US 130	60	40	Nondialysis CKD 3–5	Compare the effectiveness of educational interventions on preemptive living donor kidney transplantation	Cohort (baseline data)	Nephrology clinics	46% White, 47% black,<1% Hispanic	<18 or >70 yr old, non-English speaking, previous transplant, cancer, heart failure, severe liver disease, PVD, HIV, unstable coronary artery disease	REALM	—	25
Brice (24) 2014 US 277	—	—	Prevalent HD	Validate TILS and SILS against STOFHLA	Cross-sectional	Adults from seven HD centers	English (96%) and Spanish speakers (4%)	<18 yr old, unable to speak English or Spanish, mental impairment defined by dialysis staff, poor vision	STOFHLA, SILS and TILS (English or Spanish)	—	45 (STOFHLA), 22 (SILS)
Cavanaugh 1 (21)[a] 2010 US 480	62	56	Incident HD	Measure the prevalence and associations of limited health literacy and risk of all-cause mortality	Cohort	Adults "eligible for a patient education program" from 77 dialysis units, health literacy measured if low literacy was suspected by case manager	52% White, 50% diabetic	<18 yr old, patients on nonpermanent dialysis, known cognitive impairment, non-English speakers, nursing home residents	REALM	Mortality	32
Cavanaugh 2 (23) 2015 US 143	[52]	51	Prevalent HD	Validate BHLS against REALM and STOFHLA	Cross-sectional	Adults from four dialysis units	73% Black	<18 or >80 yr old, dialysis initiation <1 mo, non-English speakers, cognitive impairment	BHLS (0–15), REALM, and STOFHLA	—	23 (BHLS) 27 (REALM) 8 (STOFHLA)
Dageforde 1 (36) 2014 US 255	[48]	64	Incident transplant	Compare health literacy between live and deceased donor kidney transplant recipients and live kidney donors	Retrospective chart review	Transplant recipients and donors at single transplant center surveyed for health literacy preoperatively	65% White LDR (n=103) DDR (n=152)	<18 yr old, no recorded answer to BHLS	BHLS (0–15)	Donor type, education, and demographics	12 (LDRs: 9%; DDRs: 14%)

Table 1. (Continued)

Study/ Reference/ Year/ Location/ *N*	Median Age, yr [Mean]	Men, %	CKD Stage	Aim	Design	Setting and Recruitment Method	Participants	Exclusion Criteria	Health Literacy Measure	Outcome Variables Tested	Prevalence of Limited Health Literacy, %
Dageforde 2 (37) 2015 US 104	[53]	61	Dialysis (n=14) and nondialysis CKD (n=90)	Characteristics of attenders versus absentees for kidney transplant evaluation appointments	Cross-sectional	Convenience sample of patients scheduled for initial evaluation for kidney transplant at a single center	46% White	<18 yr old, non-English speakers, cognitive impairment	BHLS (0–15)	Attendance versus nonattendance	23 (14% dialysis; 24% CKD)
Devraj (38) 2015 US 150	45% over 60 yr old	47	Nondialysis CKD 1–4	Relationship between health literacy and eGFR	Cross-sectional	Adults attending follow-up nephrology outpatient appointments at a single center, given a $20 merchandise card to participate	40% White, 41% Hispanic	<21 yr old, non-English speaking, AKI, cognitive impairment defined by medical notes or if less than four on cognition screening test, poor visual acuity	NVS	eGFR (MDRD formula)	63
Foster (39) 2011 US 238	[58]	54	Prevalent dialysis (HD or PD)	Assess disaster preparedness in patients on dialysis	Cross-sectional	Adults approached during dialysis at six dialysis units	57% Black, 6% Spanish speaking, 94% English speaking	<18 yr old, unable to understand consent process	STOFHLA (English or Spanish)	Disaster preparedness	49.5
Gordon (18)[a] 2011 US 124	[47]	57	Transplant	Relationship between health literacy, transplant knowledge, and graft function	Cross-sectional	Sequential transplant recipients from a single center recruited at post-transplant clinic visit for 30-min interview		<18 yr old, non-English-speaking, visually impaired, too unwell to participate	STOFHLA and REALM-T	Demographics and graft function	9
Green (19)[a] 2011 US 260	64	57	Prevalent HD	Describe prevalence and associations of limited health literacy	Cohort (baseline data)	Patients from nine dialysis units included in an RCT of strategies for managing pain, sexual dysfunction, and depression	40% Black	<18 yr old, less than thrice-weekly dialysis, non-English speakers, cognitive impairment, considering switch to PD or transplantation	REALM	Demographics, SES, comorbidity	16
Grubbs (20)[a] 2009 US 62	[52]	66	Prevalent HD	Association of poor health literacy with access to transplantation	Cross-sectional	Adults approached during dialysis session in five dialysis units	73% Black	<18 or >75 yr old, ethnicity other than black or white, <9 mo on dialysis, previous transplant, cognitive impairment	STOFHLA	Referral for transplant evaluation, wait listing, or transplantation	32

Table 1. (Continued)

Study/ Reference/ Year/ Location/ *N*	Median Age, yr [Mean]	Men, %	CKD Stage	Aim	Design	Setting and Recruitment Method	Participants	Exclusion Criteria	Health Literacy Measure	Outcome Variables Tested	Prevalence of Limited Health Literacy, %
McNaughton (40) 2014 US 851[b]	55	57	CKD 3–5, including dialysis or transplant if eGFR<60 ml/min per 1.73 m^2	Relationship between limited health literacy and BP at ED presentation	Cross-sectional	Adults attending ED at a large quaternary hospital screened for health literacy as part of admission nursing assessment	Study included 31,902 patients, of whom 851 (3%) had kidney disease, 60% white	<18 yr old, nursing assessment or health literacy measure not completed, admitted with preeclampsia or alcohol withdrawal	BHLS (0–15)	BP at hospital presentation (in all ED attenders)	26[b]
Miller-Matero (41) 2015 US 95	—	—	Referred for transplantation (dialysis or advanced CKD)	Assess health literacy of patients referred for solid organ transplantation	Cross-sectional	Patients considered for solid organ transplantation at a single center	—	—	REALM	Demographics, cognitive impairment, reading ability, numeracy (in all organ transplant recipients)	37.8
Ricardo (42) 2014 US 2340	[58]	54	Nondialysis CKD 1–4	Association of limited health literacy with kidney function and CV risk factors	Cross-sectional	Adults with CKD recruited from seven clinical centers	52% White, 48% black	<21 or >74 yr old, polycystic kidney disease (43), Hispanic ethnicity	STOFHLA	eGFR (MDRD formula), BP, LDL cholesterol <100 mg/dl, HbA1c<7%, self-reported CV disease	16 (Black, 28%; white, 5%)
Robinson (43) 2015 US 170	[50]	59	Prevalent transplant	Validate a sun-protection education program	RCT (baseline data)	Adults from two transplant programs	35% Black, 28% Hispanic, 36% white	<2 or >24 mo after transplant, non-Spanish speakers, <18 or >70 yr old, poor vision, ethnicity other than black, white, or Hispanic	STOFHLA (English or Spanish)	—	36 (Black, 58%; Hispanic, 54%; white, 0%)
Taylor (44) 2015 UK 5520	54	62	Incident dialysis (HD or PD), incident transplant and transplant waitlisted (prevalent dialysis and nondialysis CKD)	Describe prevalence and associations of limited health literacy	Cohort (baseline data)	Adults approached for notes review and survey from all 71 United Kingdom renal units	Representative nationwide sample, 79% white, patients with CKD not on dialysis were all preemptively waitlisted for transplant	<18 or >75 yr old or unable to provide informed consent	SILS	Demographics, SES, comorbidity	16 (Dialysis, 18%; CKD wait listed, 9%; incident transplant, 12%)
Weng (45) 2013 US 252	[55]	60	Prevalent transplant	Prevalence and correlates of medication nonadherence	Cross-sectional	Adults approached during a transplant clinic visit at a single center, offered $15	58% White, 27% black, median 2.9 yr post-transplant	<6 mo Post-transplant, <18 yr old, non-English speakers, unable to consent, dual organ transplant	STOFHLA	Medication nonadherence	2.4

Table 1. (Continued)

Study/ Reference/ Year/ Location/ *N*	Median Age, yr [Mean]	Men, %	CKD Stage	Aim	Design	Setting and Recruitment Method	Participants	Exclusion Criteria	Health Literacy Measure	Outcome Variables Tested	Prevalence of Limited Health Literacy, %
Wright (47)[a] 2011 US 401	58	53	Nondialysis CKD 1–5	Measure awareness and knowledge of CKD to develop a CKD knowledge survey	Cross-sectional	Adults attending a follow-up nephrology clinic appointment at a single center, offered $10	83% White	<18 yr old, non-English speakers, kidney transplant or dialysis, vision or cognitive impairment	REALM	Kidney disease knowledge	18
Wright-Nunes (46) 2013 US 154[c]	58	54	Nondialysis CKD 1–5	Assess feasibility and effect of a physician-delivered education tool to increase CKD knowledge	Clinical trial, (baseline data)	Adults at single center asked to complete a survey (written or read aloud), offered monetary compensation	77% White, 78% CKD 3–5	<18 yr old, non-English speakers, kidney transplant or dialysis, vision or cognitive impairment	REALM	—	22

Outcome variables are listed only if statistical models included health literacy as an exposure variable. US, United States; HD, hemodialysis; PD, peritoneal dialysis; CV, cardiovascular; STOFHLA, Short Test of Functional Health Literacy in Adults; BMI, body mass index; PVD, peripheral vascular disease; REALM, Rapid Evaluation of Adult Literacy in Medicine; —, data unavailable or no outcomes tested; TILS, Two-Item Literacy Screener; SILS, Single-Item Literacy Screener; BHLS, Brief Health Literacy Screener; LDR, live donor recipient; DDR, deceased donor recipient; NVS, Newest Vital Sign; MDRD, Modification of Diet in Renal Disease; REALM-T, transplant-specific version of the Rapid Estimate of Adult Literacy in Medicine; RCT, randomized controlled trial; ED, emergency department; HbA1c, hemoglobin A1c;UK, United Kingdom; SES, socioeconomic status.

[a] Studies included in the 2012 review by Fraser *et al.* (17).

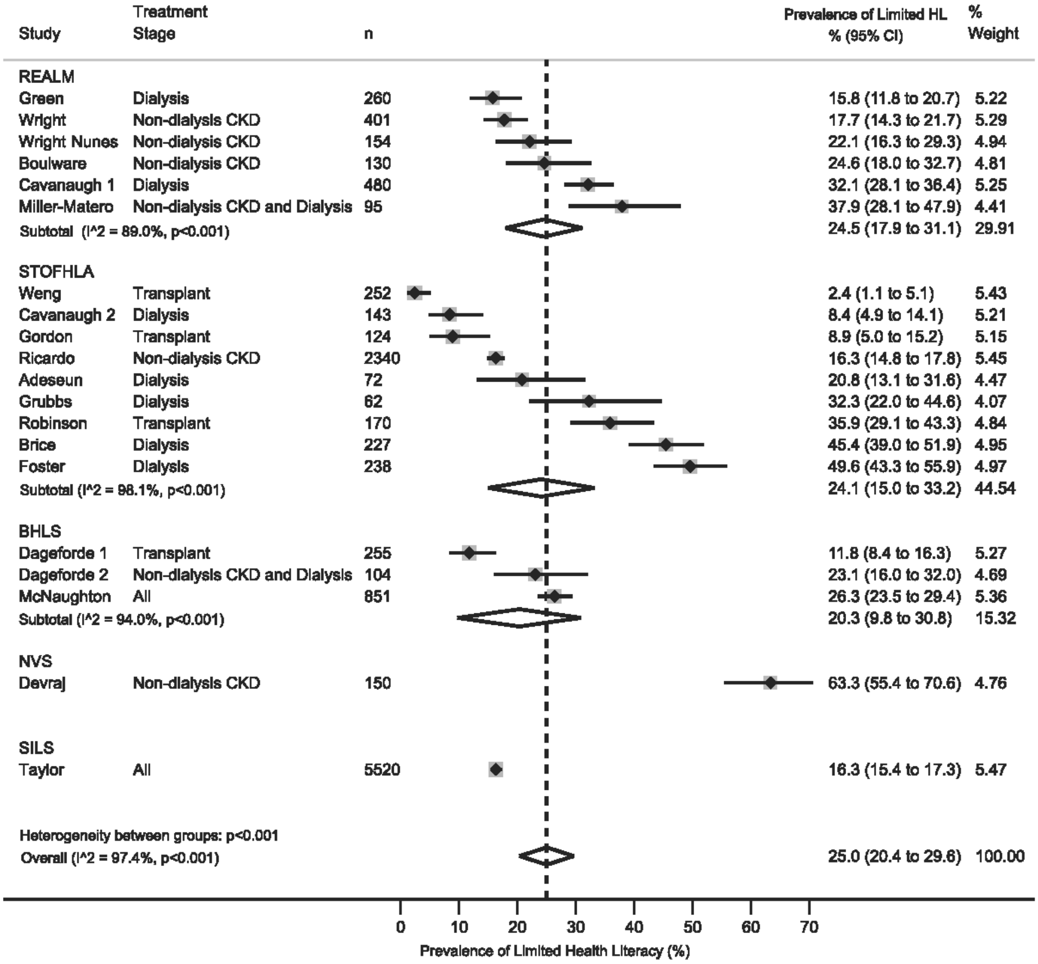
[b] Frequencies from personal communication with the authors (C. McNaughton).

[c] After excluding 401 from ref. 48.

Table 2. Health literacy measures used in studies included in this review

Health Literacy Measure	No. of Studies Using Measure (%)	Form	Approximate Time Taken (min)	Health Literacy Categorization
STOFHLA	9 (45) Three studies used both English and Spanish versions	36 Reading comprehension items selected from four choices to replace missing words in text (modified Cloze procedure)	12	0–22: Limited, 23–36: adequate
REALM	6 (30)	125 Health-related words (66 in more commonly used form) tested for pronunciation accuracy	3	0–44: Inadequate; 45–60: marginal; 61–66: adequate (limited = inadequate + marginal)
REALM-T	1 (5)	69 Kidney transplant–related terms tested for pronunciation accuracy	3	Not clearly defined
BHLS	4 (20)	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 from 3 to 15 (or 0–12 in one study [Cavanaugh *et al.*, unpublished data], Supplemental Table 1)	<1	3–8 (or 0–5): Lower; 9–14 (or 6–12): moderate/higher (<10/15 or <6/12 indicates limited health literacy)
NVS	1 (5)	Six-item assessment of reading comprehension from an ice cream nutrition label,	6 maximum (average 2.9) (56)	0–1: High likelihood marginal/inadequate; 2–3: possible marginal/inadequate; 4–6: adequate (score <4 indicates limited health literacy [39])
SILS	2 (10) (one used English and Spanish versions)	"How often do you need to have someone help you when you read instructions, pamphlets or other written material from your doctor or pharmacy" answered on a 5-point Likert scale from 1 (never) to 5 (always)	<1	<3: Adequate; ≥3: limited
TILS	1 (5) (English or Spanish)	Two questions. What was the last (educational) grade you completed? Can you estimate your reading ability with one of the following: "I frequently read complete books," "I read the newspaper," "I occasionally need help with the newspaper," or "I frequently need help with the newspaper"; scored from −4 to +5	<1	Sensitivity/specificity of different cutoff points was tested; use of TILS>1 to indicate limited health literacy is suggested

STOFHLA, Short Test of Functional Health Literacy in Adults; REALM, Rapid Evaluation of Adult Literacy in Medicine; REALM-T, transplant-specific version of the Rapid Estimate of Adult Literacy in Medicine; BHLS, Brief Health Literacy Screener; NVS, Newest Vital Sign; SILS, Single-Item Literacy Screener; TILS, Two-Item Literacy Screener



Study	Treatment Stage	n	Prevalence of Limited HL % (95% CI)	% Weight
REALM				
Green	Dialysis	260	15.8 (11.8 to 20.7)	5.22
Wright	Non-dialysis CKD	401	17.7 (14.3 to 21.7)	5.29
Wright Nunes	Non-dialysis CKD	154	22.1 (16.3 to 29.3)	4.94
Boulware	Non-dialysis CKD	130	24.6 (18.0 to 32.7)	4.81
Cavanaugh 1	Dialysis	480	32.1 (28.1 to 36.4)	5.25
Miller-Matero	Non-dialysis CKD and Dialysis	95	37.9 (28.1 to 47.9)	4.41
Subtotal (I^2 = 89.0%, p<0.001)			24.5 (17.9 to 31.1)	29.91
STOFHLA				
Weng	Transplant	252	2.4 (1.1 to 5.1)	5.43
Cavanaugh 2	Dialysis	143	8.4 (4.9 to 14.1)	5.21
Gordon	Transplant	124	8.9 (5.0 to 15.2)	5.15
Ricardo	Non-dialysis CKD	2340	16.3 (14.8 to 17.8)	5.45
Adeseun	Dialysis	72	20.8 (13.1 to 31.6)	4.47
Grubbs	Dialysis	62	32.3 (22.0 to 44.6)	4.07
Robinson	Transplant	170	35.9 (29.1 to 43.3)	4.84
Brice	Dialysis	227	45.4 (39.0 to 51.9)	4.95
Foster	Dialysis	238	49.6 (43.3 to 55.9)	4.97
Subtotal (I^2 = 98.1%, p<0.001)			24.1 (15.0 to 33.2)	44.54
BHLS				
Dageforde 1	Transplant	255	11.8 (8.4 to 16.3)	5.27
Dageforde 2	Non-dialysis CKD and Dialysis	104	23.1 (16.0 to 32.0)	4.69
McNaughton	All	851	26.3 (23.5 to 29.4)	5.36
Subtotal (I^2 = 94.0%, p<0.001)			20.3 (9.8 to 30.8)	15.32
NVS				
Devraj	Non-dialysis CKD	150	63.3 (55.4 to 70.6)	4.76
SILS				
Taylor	All	5520	16.3 (15.4 to 17.3)	5.47
Heterogeneity between groups: p<0.001				
Overall (I^2 = 97.4%, p<0.001)			25.0 (20.4 to 29.6)	100.00

Figure 2. | Overall pooled prevalence of limited health literacy is 25%; there was no significant difference between pooled prevalence estimates from studies using REALM, STOFHLA and BHLS. Dashed reference line indicates pooled prevalence value. BHLS, Brief Health Literacy Screener; 95% CI, confidence interval; HL, health literacy; NVS, Newest Vital Sign; REALM, Rapid Evaluation of Adult Literacy in Medicine; SILS, Single-Item Literacy Screener; STOFHLA, Short Test of Functional Health Literacy in Adults.

with authors. Studies included a median of 198.5 patients (interquartile range [IQR], 128.5–260).

One study included live kidney donors (36), and one included recipients of solid organ transplants of different types (41) in addition to patients with CKD; subgroup information was available from published data. One study (40) measured health literacy in 46,000 emergency department attendees, including 851 with CKD (40). The authors provided data on this subgroup by personal communication (C. McNaughton).

Table 2 summarizes the health literacy measures and definitions of limited health literacy used.

One study included all emergency department attendees (40), and one aimed to approach all eligible patients across the United Kingdom (44). Two studies surveyed patients from clinical trials for primary objectives that were unrelated to health literacy (19,34). All others recruited from clinical environments without efforts to obtain a sample representative of a target CKD population. Two studies surveyed patients with CKD at transplant assessment clinics (37,41), whereas one excluded patients listed for transplant (19). Three studies reported offering a monetary gift to participants (45–47). At least 11 studies excluded patients with cognitive impairment. One study included patients deemed suitable for an educational intervention (21). Six studies specified an upper limit for age, ranging from 74 to 80 years old (20,23,35,42–44).

Ethnicity data were unavailable for one study (total of 95 patients) (41), and age data were unavailable for two studies (total of 322 patients) (24,41). From the remaining data, the median proportion of participants of nonwhite ethnicity was 48% (IQR, 23%–64%), and mean or median age ranged from 47 to 72 years old. In some United States studies, the majority of study participants had black ethnicity (20,23,39). One study excluded patients with Hispanic ethnicity (42). Twelve studies included only

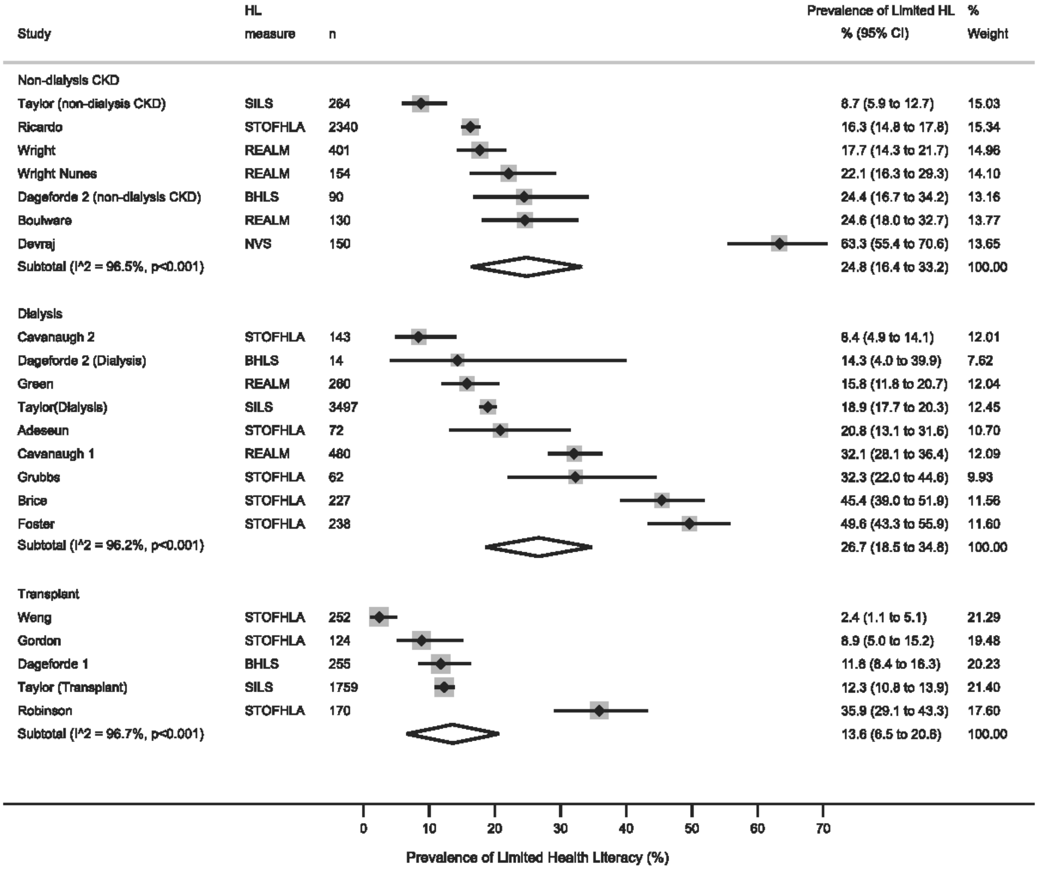


Figure 3. | **The pooled prevalence of limited health literacy is significantly lower in transplanted patients compared to those with nondialysis CKD or on dialysis.** Two studies where treatment stage was not defined are not shown. BHLS, Brief Health Literacy Screener; 95% CI, confidence interval; HL, health literacy; NVS, Newest Vital Sign; REALM, Rapid Evaluation of Adult Literacy in Medicine; SILS, Single-Item Literacy Screener; STOFHLA, Short Test of Functional Health Literacy in Adults.

English speakers. Three studies included Spanish speakers and used health literacy measures translated into Spanish (24,39,43).

The median prevalence of limited health literacy by study was 23% (IQR, 16%–33%). The overall pooled prevalence of limited health literacy was 25% (95% CI, 20% to 30%). A high degree of heterogeneity was present between studies (I^2=97.4%).

Figure 2 shows a Forest plot of the prevalence of limited health literacy in all 20 studies with subgroup analysis by health literacy measure. Studies using the Newest Vital Sign (NVS) and the Single-Item Literacy Screener (SILS) reported significantly different prevalence values, but only one study used each measure (38,44). These prevalence values contributed to the significant overall heterogeneity in limited health literacy prevalence between studies using different measures ($P<0.001$). However, when studies using the Rapid Estimate of Adult Literacy in Medicine (REALM), the STOFHLA and the Brief Health Literacy Screen (BHLS) were compared alone, no significant between-group heterogeneity was detected (P=0.80).

Figure 3 shows subgroup analysis by CKD treatment stage, excluding two studies where subgroup information was unavailable (40,41). The pooled prevalence of limited health literacy was 25% (95% CI, 16% to 33%) among patients with nondialysis CKD, 27% (95% CI, 19% to 35%) among patients on dialysis, and 14% (95% CI, 7% to 21%) among patients with transplants. Overall, there was significant between-group heterogeneity (P=0.03), although this seems to be related to the lower prevalence of limited health literacy in patients with transplants: when patients with nondialysis CKD and patients on dialysis were compared separately, no significant between-group heterogeneity was present (P=0.80).

Univariate metaregression analysis showed a significant association between the proportion of nonwhite participants in a study and the prevalence of limited health literacy (β=0.35; 95% CI, 0.00 to 0.69; P=0.04). This equates to a 3.5% increase in the prevalence of limited health literacy for every 10% increase in the proportion of nonwhite participants. Average age of study participants was not significantly associated with the prevalence of

Table 3. Summary of univariate and multivariate associations with limited health literacy.

		Demographics							Socioeconomic								Comorbidity											Biochemistry				Drugs			Dialysis					Transplant				Knowledge/education						
Univariate Associations		Older age	Male	Ethnicity	English Fluency	Veteran	Support person	Renal unit	Non-Employment	Lower Income	Lower educational level	Non car ownership	Non-married	More children	Insurance	Other SES measure	Lower Physical Activity	Kidney disease duration	Higher comorbidity index	CV disease	Diabetes	BMI	Hypertension	Higher Blood Pressure	Hyperlipidaemia	Psychosis	Smoking	Lower eGFR	Proteinuria	Albumin	HbA1c	ACE/ARB	Insulin use	Aspirin	Dialysis initiation	Dialysis adequacy (Kt/V)	Fistula (compared to catheter)	Age at dialysis start	Dry Weight	Deceased-donor (vs live)	Non pre-emptive transplant	Time since transplant	Previous transplant	Lower objective knowledge	Lower percieved health	Kidney education resource use	Nephrologist care	Aware of diagnosis	Know someone with CKD	Increased mortality
Adenseun				• *						•	•																																							
Cavanaugh 1				• †							•		•																	•									•											•
Dageforde 1																																								•										
Devraj				• ‡						•	•				•																																			
Gordon										•	•		•																																					
Green				• *		•				•	•								•																		•													
Grubbs		•								•	•																																							
Ricardo		•		• †						•	•						•			•	•		•					•	•				•												•					
Taylor		•		• §	•				•		•		•	•					•							•														•	•									
Wright																																												•						
Multivariate Associations																																																		
Study	**Model**																																																	
Adeseun	1	▨	▨	▨ • *						▨ •	▨																																							
	2	▨	▨	▨						▨	▨													▨ •																										
Cavanaugh 1	1	▨	▨ •	▨ • †							▨ •		▨								▨	▨								▨						▨														
	2	▨	▨	▨																	▨																													▨ •
Dageforde 1		▨	▨	▨							▨ •																													▨ •										
Devraj										▨	▨				▨	▨		▨	▨		▨ •							▨ •																						
Gordon		▨	▨	▨					▨	▨ •	▨ •		▨ •																											▨		▨	▨							
Green				▨ • *		▨ •				▨	▨ •																																							
Grubbs		▨ •	▨	▨			▨			▨ •	▨ •								▨																			▨												
Ricardo	1	▨	▨	▨				▨			▨										▨	▨		▨			▨	▨ •			▨	▨	▨														▨			
	2	▨	▨	▨				▨												▨ •	▨	▨		▨	▨		▨	▨			▨	▨	▨	▨	▨															
Taylor		▨	▨	▨	▨ •				▨ •		▨ •	▨ •							▨ •							▨ •																								
Wright		▨																										▨																▨ •		▨		▨	▨	

Markers indicate statistically significant associations with limited health literacy. Shaded boxes indicate covariates included in multivariate models. *, African-American; †, Non-white; ‡, Hispanic; §, South Asian, Chinese.

limited health literacy (β=1.05; 95% CI, −0.5 to 2.6; P=0.40).

Two studies used multiple health literacy measures, reporting three limited health literacy prevalence values each (23,24). In the above analyses, results defined by the STOFHLA were used for both studies. Repeated analyses using each of nine possible combinations of limited health literacy prevalence values did not lead to a change in the significance of the above results, except for metaregression by proportion of nonwhite participants. In four of nine combinations, this association was no longer statistically significant. A further sensitivity analysis included 11 conference abstracts in addition to the 20 published papers included here (Supplemental Material, Supplemental Table 1). Analysis of results from all 31 studies showed a pooled prevalence of limited health literacy of 25% and no change in the pattern of results as presented above. However, when abstracts were included, the significance of the association between proportion of nonwhite participants and limited health literacy prevalence increased (P=0.01).

Table 3 summarizes significant associations with limited health literacy and covariates included in multivariate models. A large variety of variables was tested. In ten studies that undertook multivariate analysis, the only demographic factors consistently and independently associated with limited health literacy were ethnicity (19,21,34) and markers of lower SES, including income (18,20,34) and lower educational level (18–21,36,44). Independent associations were also reported between limited health literacy and older age (20), men (21), lower English fluency (44), individual comorbidities (38,42), and higher comorbidity score (44).

In patients with nondialysis CKD, two studies reported independent associations between limited health literacy and lower eGFR (38,42). Limited health literacy was associated with deceased donor transplantation (compared with live donor) and transplantation after dialysis start (compared with preemptive) (44). One study reported an independent association between limited health literacy and mortality (21).

Discussion

This systematic review of literature published until mid-2016 shows the significant expansion of health literacy research in CKD. Fifteen studies published since 2012 were identified, and 12,324 patients have now been studied compared with 1405 in the 2012 review by Fraser *et al.* (17). Geographical variation of studies remains limited: only one was from outside the United States. The pooled prevalence of limited health literacy in this analysis was 25%, similar to 23% in the 2012 review. The six new studies of patients with nondialysis CKD and four new studies of patients with transplants allowed meta-analysis by patient group, confirming the reduced prevalence of limited health literacy among patients with transplants, which has been reported in individual studies (44). Four new studies used the BHLS, and comparison with studies using the REALM and the STOFHLA showed no significant difference in limited health literacy prevalence, increasing the confidence with which results can be compared between studies of patients with CKD using these health literacy measures.

The lower prevalence of limited health literacy among patients with kidney transplants has several possible explanations. Limited health literacy may directly impede effective clinician-patient communication, reducing the likelihood of clinically suitable patients understanding the benefits of transplantation and pursuing it as a treatment option. Because of associations with low SES, limited health literacy has been implicated as a possible mediating factor in reducing access to transplantation. However, mechanisms by which low SES associates with reduced access to transplantation (48) are complex [and in the United States, include reduced access to immunosuppressant drugs (49)]. The associations of both limited health literacy (44) and SES (50) with increased comorbidity add further complexity: patients with limited health literacy and low SES may, in fact, be less suitable for transplantation for clinical reasons. These complex associations warrant further investigation.

A higher proportion of individuals with nonwhite ethnicity was significantly correlated with a higher prevalence of limited health literacy. Because 19 of 20 studies were from the United States, nonwhite ethnicity represents patients with black or Hispanic ethnicity. Nonwhite ethnicity in the United States has established complex associations with low SES (51) and poorer health outcomes (52), and therefore, this may represent confounding by SES and comorbidity. Although all three studies that reported independent associations between ethnicity and limited health literacy adjusted for SES (19,21,34), only one adjusted for comorbidity (as presence or absence of diabetes) (21). Age of study participants did not seem to influence the prevalence of limited health literacy.

Even after adjustment for treatment stage, health literacy measure, age, or ethnicity, there was significant residual heterogeneity in the prevalence of limited health literacy between studies. Study methodology had potential to contribute to this heterogeneity. Sample size was mostly small (median =189). The majority of studies recruited patients by convenience in clinical environments, which may result in participation bias. Studies that included only patients who had been referred for transplantation (or excluded those who had been referred) are likely to produce biased estimates of limited health literacy prevalence (19,46,47). Patients with cognitive impairment or language difficulties may show a reduction in understanding and be falsely classified as having limited health literacy. Many studies excluded those with cognitive impairment for this reason, but some did not, and no associations between cognitive impairment and health literacy were tested. The approach to patients whose first language is not English could also bias results. Some studies excluded non-English speakers who would be more likely to have limited health literacy because of the association with nonwhite ethnicity and lower SES. Others used translated versions of health literacy measures to allow inclusion of non-English speakers. However, non-English versions of health literacy measures have not been validated extensively, and comparison of results between English and non-English versions is problematic because of inherent differences between English-speaking and non–English-speaking populations (53). Other studies used English health literacy measures for all participants, which could result in patients being falsely classified as having low health literacy because of poor understanding related to language.

The different health literacy measures used vary in their method of assessment and the skills that are assessed. This limits comparability of results between studies. The REALM and the STOFHLA are direct assessments of pronunciation and reading comprehension, whereas the screening tools the BHLS and the SILS focus on patient perception of their level of understanding. It is reassuring that the BHLS produced similar prevalence estimates to the REALM and the STOFHLA in our meta-analysis, although health literacy screening tools have been shown in validation studies of CKD and other populations to lack sensitivity and specificity in detecting limited health literacy defined by the REALM or the STOFHLA (23,24,33,54). Screening tools benefit from short administration times, and therefore, they are more practical for use in large-scale cohort studies or screening in clinical practice. The NVS (55) is the only measure used here that assesses poor numeracy: a common characteristic of patients with CKD (56) and other chronic diseases (57) that may impair patients' ability to dose medications, follow dietary advice, and keep appointments (58).

Systematic reviews of health literacy prevalence in other populations report similar findings. A 2005 review of United States studies reported a pooled prevalence of 26% "low" health literacy associated with lower educational level, black ethnicity, and older age (59). A review of health literacy in patients with musculoskeletal diseases found between 7% and 42% low health literacy associated with lower SES (60).

This review benefits from a comprehensive search strategy using updated search terms. Eligibility criteria were clearly defined. We sought and received valuable communication from many authors, enhancing the quality of the review. A sensitivity analysis, which included data from conference abstracts, identified no major differences in results. There are several limitations. First, studies were of low or moderate quality because of small sample size, single-center samples, and nonrepresentative sampling methods. Second, studies using newer measures that measure multiple aspects of health literacy on separate scales (13) but do not define limited health literacy could not be included. Third, most studies used cross-sectional data, and the association of limited health literacy with increased mortality (21) could result in survivorship bias and an underestimate of limited health literacy prevalence in cross-sectional studies. Fourth, metaregression to account for age and ethnicity differences between studies was especially limited by missing data, and multivariate metaregression was not possible. However, a positive association was still shown between nonwhite ethnicity and limited health literacy prevalence, despite this lack of power. Fifth, ages of study participants were available as mean or median, limiting the reliability of metaregression analysis by age. Sixth, one study showed a lower prevalence of limited health literacy among those listed for transplantation compared with patients on incident dialysis (44), but this association could not be investigated here because of the absence of consistent data on waitlisting status.

Clinicians should recognize that one quarter or more of patients with CKD have reduced health literacy skills. Standard shared decision-making and self-management initiatives may not be suitable (11,61). Furthermore, those with limited health literacy have an increased burden of disease and treatment due to comorbidity and may lack social resources required to manage disease because of low SES (7,8). In the face of these challenges, health literacy–sensitive communication methods, educational tools, and decision aids may be key to improving clinical outcomes and may have a role in reducing inequity in access to transplantation.

The expansion of health literacy research in CKD since the last review is welcome, but further work is required to use this knowledge to promote improved clinical outcomes. All health literacy research will be facilitated by evidence-based consensus on the optimal tools to measure health literacy. Prospective studies are required to examine the effect of limited health literacy on health care service use, CKD management, and RRT modality choice (including nondialysis care). Interactions between health literacy and other patient attributes, such as capacity (8) and patient activation (62) ,warrant investigation. Knowledge of the mechanisms by which limited health literacy could impair navigation of the CKD care pathway will inform enhanced communication methods and modified approaches to shared decision making and self-management. By improving patients' understanding, these initiatives would aim to reduce inequity of care and improve the health of the CKD population.

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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 socio-economic status and non-white ethnicity, limited health literacy may promote health inequity.

Methods. We performed a systematic review of quantitative studies of health literacy and clinical outcomes among adults with CKD.

Results. A total of 29 studies (13 articles; 16 conference abstracts) were included. One included non-USA patients. Of the 29 studies, 5 were cohort studies and 24 were cross-sectional. In all, 18 300 patients were studied: 4367 non-dialysis CKD; 13 202 dialysis; 390 transplant; 341 unspecified. Median study size was 127 [interquartile range (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 hospitalizations, 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 socio-economic 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.

Keywords: chronic kidney disease, dialysis, health literacy, transplantation

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 socio-economic 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 summarize the evidence for associations between reduced health literacy and patient outcomes in CKD.

MATERIALS AND METHODS

The review protocol was registered with the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO; reference: CRD42016049172).

D.M.T. and S.F. assessed English language studies of any design for inclusion by three criteria:

(i) At least 50 adults over 18 years of age with CKD were included.
(ii) A validated tool was used to quantitatively describe an individual's overall health literacy on a single scale.
(iii) Associations were tested between health literacy and health outcomes among patients with CKD.

CKD was defined within studies by diagnosis code, estimated glomerular filtration rate (eGFR) 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 data, 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 a continuous measure and clinical outcomes. The health literacy measures used and definitions of limited health literacy are shown in Table 1.

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 2011–16 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 litera*' 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.

D.M.T. recorded and summarized 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 that were found. Results from cohort studies were presented separately from the results of cross-sectional studies. Outcome measures were categorized 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 summarized, with 95% confidence intervals (95% CIs). Meta-analysis was not possible because of the diverse range of outcome measures tested. Study quality was assessed using a pre-agreed scoring system. D.M.T. and S.F. 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 data. 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. In all, 29 studies were eligible for inclusion [13, 15–42], summarized in Table 3. There was full agreement between the two reviewers as to which studies met the inclusion criteria. A total of 13 published articles [15–17, 21, 24–27, 30, 39–42] and 16 conference abstracts [13, 18–20, 22, 23, 28, 29, 31–38] were included. Of the 29 studies, 5 were cohort studies (2 published articles [16, 17] and 3 conference abstracts [13, 18, 19]); 24 were cross-sectional studies, 1 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) [13]. All others reported exclusively on patients from the USA.

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

Health literacy measure	Number of studies using measure (%)	Form	Approximate time taken	Health literacy categorization
Short test of functional health literacy in adults (STOFHLA)	10 (34)	36 reading comprehension items—select from four choices to replace missing words in text (modified Cloze procedure)	12 min	0–22: limited 23–36: adequate
Rapid estimate of adult health literacy in medicine (REALM)	9 (31)	125 health-related words (66 in more commonly used form) tested for pronunciation accuracy	3 min	0–44: inadequate 45–60: marginal 61–66: adequate (limited = inadequate + marginal)
REALM-T	2 (7)	Transplant-specific version of REALM. 69 kidney transplant-related terms tested for pronunciation accuracy	3 min	Not clearly defined
REALM-SF	3 (10)	Short Form of REALM. Seven health-related words tested for pronunciation accuracy	2–3 min	0–3: inadequate 4–6: marginal 7: adequate
Brief health literacy 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 Cavanaugh *et al.* [13])	<1 min	3–8 (or 0–5): lower 9–14 (or 6–12): moderate/higher (<10/15 or < 6/12 indicates limited health literacy)
Newest Vital Sign (NVS)	4 (14)	Six-item assessment of reading comprehension from an ice-cream nutrition label	6 min maximum (average 2.9 min) in Weiss *et al.* [14]	0–1: high likelihood marginal/inadequate 2–3: possible marginal/inadequate 4–6: adequate (here, <4 deemed limited health literacy in Devraj *et al.* [15])

In total, 18 300 patients were studied, 14 682 of whom were included in five cohort studies. A total of 4367 patients from 12 studies had non-dialysis CKD. Altogether 13 202 dialysis patients were studied in 13 studies and 390 transplant patients were studied in 3 studies. Of the dialysis patients, a maximum of 84 received peritoneal dialysis. Three studies included patients at multiple treatment stages [20, 24, 30]. For two studies describing 341 patients [20, 30], 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 [interquartile range (IQR) 92–238].

The health literacy measures used and the associated definitions of limited health literacy are summarized in Table 1. Two studies used more than one measure.

Two studies included recruits to established clinical trials [17, 19]; the remainder selected patients from clinical environments without randomization or measures to ensure a representative sample had been obtained. Sixteen conference abstracts were included. 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 to 72 years. For 23 studies where gender data were available, the median proportion of male participants per study was 54% (IQR 49.5–57.5). Ethnicity of participants was not stated for 8 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 [13, 17, 23] and high for 1 study [18].

In Table 2, the numerous outcome measures that 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 summarized in Tables 4 and 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 (Table 3 and 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) [13]. Two cohort studies reported on patients with non-dialysis CKD [18, 19]. One study of 2392 patients with CKD Stage 1–4 showed independent associations between limited health literacy and hospitalizations and atherosclerotic events (defined as myocardial infarction, stroke or peripheral-vascular disease), with adjustment for socio-economic status, comorbidity and demographics. No association was found between health literacy and mortality in this study. Another cohort study showed a significant

Table 2. Outcome variables tested for association with health literacy. (Bold indicates variables tested in cohort studies).

Patient group	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 that 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	Attendance versus non-attendance at transplant assessment	BP	Lipids	**Progression to ESRD**
	Objective kidney disease knowledge		Tobacco use	eGFR	**Dialysis initiation**
	Perceived kidney disease knowledge		Waist-hip ratio		**Atherosclerotic event (MI, stroke, PVD)**
	Patient satisfaction with clinician communication		Body mass index		**Hospitalization rate**
	Sodium knowledge		Dietary intake		**Mortality**
	Knowledge of restricted foods				
	Awareness of CKD				
Dialysis	Improvement in dialysis/transplant knowledge after education	Infection episodes	BP	Haemoglobin	Time to transplant referral
	Disaster preparedness	**Hospitalizations**	Dialysis catheter use	Haematocrit	Time to transplant listing
	Medication label understanding	**ED attendances**	IDWG	Transferrin saturation	**Mortality**
	Decision-making capacity	**Missed dialysis sessions**		Calcium	Kidney transplantation
	Medicines management capacity	Attendance versus non-attendance at transplant assessment		Phosphate	
	Self-reported medication adherence			Intact parathyroid hormone	
	Dialysis knowledge			Albumin	
				Dialysis adequacy (Kt/V)	
Transplant	Medication non-adherence (by survey measure)			Transplant function	
	Decision-making capacity				

BP, blood pressure; ED, emergency department; eGFR, estimated glomerular filtration rate; IDWG, inter-dialytic weight gain; MI, myocardial infarction; PVD, peripheral vascular disease.

univariate association between limited health literacy and hazard of dialysis initiation among 74 patients with CKD Stages 3 and 4, but no significant difference in the rate of hospitalization [19].

Three cohort studies reported on dialysis patients [13, 16, 17]. A study of 260 prevalent haemodialysis patients showed independent associations between limited health literacy and hospitalizations, missed dialysis sessions and emergency department attendances, after adjustment for demographics, income and comorbidity [17]. 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 [16] and 11 476 prevalent haemodialysis patients from multiple countries [13]. One of these did not include adjustment for socio-economic status [16] and the other did not include adjustment for comorbidity [13].

In results from cross-sectional studies, lower health literacy was independently associated with lower eGFR [15] and lower perceived [41] and objective [40] kidney disease knowledge among patients with non-dialysis CKD. Among dialysis patients, limited health literacy was independently associated with higher blood pressure (diastolic and mean arterial pressure) [21] and longer time to transplant referral [27] after adjustment for demographics and socio-economic status. An independent association between limited health literacy and dialysis catheter use was found in one study [23] without adjustment for socio-economic status. This finding conflicted with another study showing higher fistula use among those with limited health literacy by univariate analysis [17]. Three other studies tested for an association between health literacy and type of haemodialysis access, but found no significant associations [16, 32, 37].

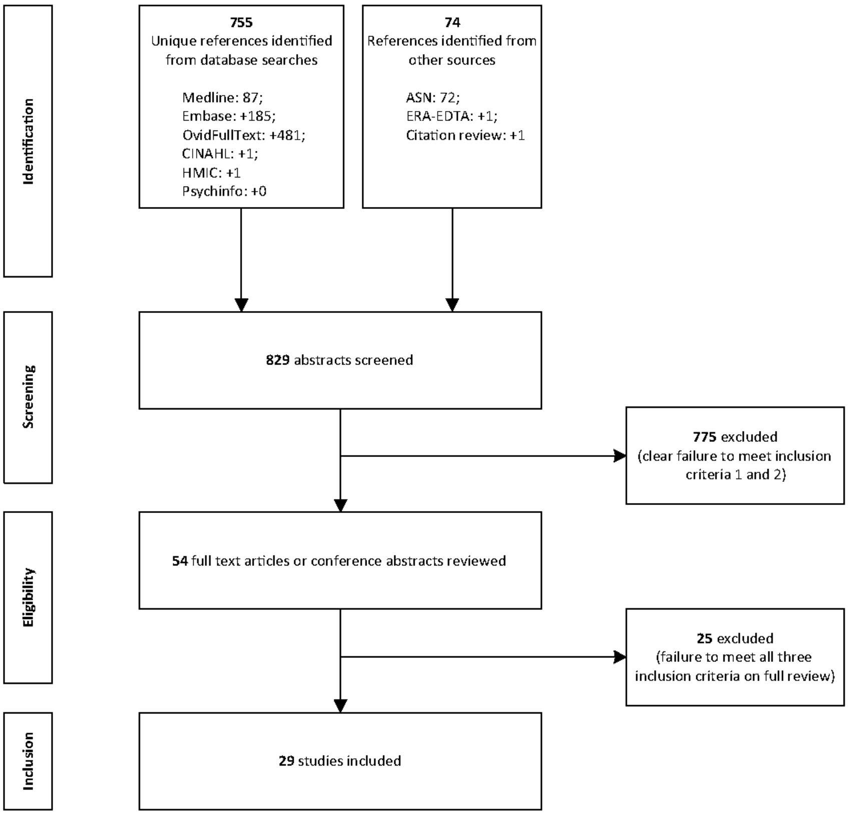

FIGURE 1: Study identification process. Citations for the 25 studies that were fully reviewed, but not included are shown in the Supplementary data. ASN, American Society of Nephrology Kidney Week; CINAHL, Cumulative Index to Nursing and Allied Health Literature; ERA-EDTA, European Renal Association–European Dialysis and Transplant Association Congress; HMIC, Health Management Information Consortium.

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 hospitalizations and cardiovascular events in non-dialysis CKD patients, and with reduced dialysis adherence, hospitalization 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 [33, 40, 41]. One cohort study reported increased risk of hospitalizations [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 with those with adequate health literacy [18]. 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) [15], this finding was not supported by a high-quality cohort study that found no significant association between limited health literacy and the incidence of end-stage renal disease (ESRD) [hazard ratio (HR) 1.10; 95% CI 0.74–1.60] [18].

Dialysis patients with limited health literacy were found to be at increased risk of mortality compared with those with adequate health literacy in analyses from two cohort studies (HR 1.65; 95% CI 1.28–2.12 and HR 1.54; 95% CI 1.01–2.36)

Table 3. Summary characteristics of included studies

Study design	Study	Year	*n*	Median age (years) [mean]	Male (%)	CKD stage	Aim	Setting and recruitment method	Participants	Exclusion criteria	Health literacy measure	Outcome variables tested	Follow-up time (for cohort studies)
Cohort	Cavanaugh *et al.* [16]	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)
Cohort	Cavanaugh *et al.* [13] (abstract)	2015	11 476	–	–	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[a]	–	None stated	BHLS (0–12)	Mortality by adjusted hazard ratio	Not stated
Cohort	Green *et al.* [17]	2013	260	62	58	Prevalent HD	Examine associations of LHL with dialysis adherence and health resource use	Patients from nine 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 hospitalizations. Kidney transplantation, mortality	12–24 months
Cohort	Lora *et al.* [18] (abstract)	2016	2392	–	–	Non-dialysis CKD 1–4	Identify clinical outcomes associated with LHL	Non-Hispanic black and white	–	Hispanic patients	STOFHLA	Incident ESRD, atherosclerotic events, hospitalizations, mortality	3.5 years median
Cohort	Singla *et al.* [19] (abstract)	2016	74	[58]	57	Non-dialysis CKD 3–4	Identify prevalence and associations of LHL	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	Hospitalizations Dialysis initiation	24 months
Intervention pilot	Basu *et al.* [20] (abstract)	2015	214	–	–	Non-dialysis and dialysis CKD	Pilot of education tool with pre- and post-intervention knowledge survey	Three kidney transplant centres	–	None stated	NVS	Improvement in dialysis/transplant knowledge	Post-intervention

Cross-sectional	Adeseun *et al.* [21]	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 with 50% of those with adequate HL	Previous coronary revascularization, cardiac devices or weight >350 lbs	STOFHLA	BP, lipid profile, waist-to-hip ratio, BMI, tobacco use	–
Cross-sectional	Blandon *et al.* [22] (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	–
Cross-sectional	Cavanaugh *et al.* [23] (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	–
Cross-sectional	Dageforde *et al.* [24]	2015	104	[53]	61	Dialysis ($n = 14$) and non-dialysis CKD ($n = 90$)	Characteristics of attenders versus 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 versus non-attendance	–
Cross-sectional	Devraj *et al.* [15]	2015	150	45% over 60	47	Non-dialysis CKD 1–4	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	–
Cross-sectional	Foster *et al.* [25]	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	–
Cross-sectional	Gordon and Wolf [26]	2009	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-min interview		<18; non-English-speaking; visually impaired, too unwell to participate	STOFHLA and REALM-T	Transplant function	–
Cross-sectional	Grubbs *et al.* [27]	2009	62	[52]	66	Prevalent HD	Association of poor HL with access to transplantation	Adults approached during dialysis session in five 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 transplant evaluation, time from referral to listing (measured retrospectively)	–

Continued

Table 3. Continued

Study design	Study	Year	*n*	Median age (years) [mean]	Male (%)	CKD stage	Aim	Setting and recruitment method	Participants	Exclusion criteria	Health literacy measure	Outcome variables tested	Follow-up time (for cohort studies)
Cross-sectional	Jain *et al.* [28] (abstract)	2005	92	63		Prevalent HD	Measure HL in prevalent HD patients. Assess relationship with demographics and quality measures	HD outpatients at two dialysis units	40% white	None stated	REALM	IDWG, Phos, *Kt/V*	–
Cross-sectional	Jang *et al.* [29] (abstract)	2014	110	>65 (exact figure not known)	58	Prevalent HD	Compare medication label understanding to REALM-SF	Adults from three dialysis centres	83% white. 11% had not completed high school	<18; non-English speaking, 'unable to reasonably manage medications'	REALM-SF	Medication label understanding	–
Cross-sectional	Kazley *et al.* [30]	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 outpatient clinics	Pre-transplant dialysis, transplant or planned vascular access procedure	Non-English speaking	NVS and REALM-T	DMCAT decision-making tool	
Cross-sectional	Nelson *et al.* [31] (abstract)	2015	208	[72]	56	Non-dialysis CKD 3b–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	
Cross-sectional	Posadas et al. [32] (abstract)	2011	83	–	43	Prevalent HD	Identify patient factors associated with dialysis catheter use	Single HD unit	–	None stated	STOFHLA	HD catheter use	–
Cross-sectional	Puher *et al.* [33] (abstract)	2014	512	[66]	50	Non-dialysis CKD 3–5	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	–
Cross-sectional	Rao *et al.* [34] (abstract)	2016	52	–	–	Non-dialysis CKD 4–5	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	–
Cross-sectional	Segal *et al.* [35] (abstract)	2016	108	[60]	56	Non-dialysis CKD 1–5	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)	–

Cross-sectional	Shirsalkar *et al.* [36] (abstract)	2014	56	–	–	Prevalent HD	Identify patient factors associated with dialysis adherence and IDWG	–	Veterans	None stated	STOFHLA	IDWG, dialysis knowledge	–
Cross-sectional	Singh *et al.* [37] (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, hospitalizations, vascular access	–
Cross-sectional	Vourakis *et al.* [38] (abstract)	2012	122	[69]	54	Prevalent HD	Measure associations between HL and Phos and Alb	Convenience sample from three urban HD facilities	22% black	None stated	REALM-SF	Phos	–
Cross-sectional	Weng *et al.* [39]	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)	–
Cross-sectional	Wright *et al.* [40]	2011	401	58	53	Non-dialysis CKD 1–5	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	Wright Nunes *et al.* [41]	2011	399 (all included in Wright)	[57]	53	Non-dialysis CKD 1–5	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% CKD 3–5	<18; non-English speakers, kidney transplant or dialysis, vision or cognitive impairment	REALM	Perceived kidney disease knowledge, patient satisfaction with clinician communication	–
Cross-sectional	Wright Nunes *et al.* [42]	2015	155	57	54	Non-dialysis CKD 1–5	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	–

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[a] Australia, New Zealand, Canada, UK, USA, Belgium, France, countries of the former Gulf Cooperation Council (GCC), Germany, Italy, Japan, Russia, Span, Sweden and Turkey.

AKI, acute kidney injury; Alb, serum albumin; BHLS, Brief Health Literacy Screen; BMI, body mass index; BP, blood pressure; Ca, serum calcium; CV, cardiovascular; CVD, cardiovascular disease; DOPPS, Dialysis Outcomes and Practice Patterns Study; ED, emergency department; ESRD, End-Stage Renal Disease; STOFHLA, Short Test of Functional Health Literacy in Adults; NVS, Newest Vital Sign; DMCAT, Decision-Making Capacity Assessment Tool; HD, haemodialysis; Hb, haemoglobin; Hct, haematocrit; HL, health literacy; IDWG, intra-dialytic weight gain; iPTH, intact parathyroid hormone; REALM, Rapid Estimate of Adult Literacy in Medicine; LD, Living Donor; LHL, limited health literacy; MDRD, Modification of Diet in Renal Disease; PD, peritoneal dialysis; Phos, serum phosphate; RCT, randomized controlled trial; TS, transferrin saturation.

Table 4. Summary of tested associations between limited health literacy (or lower health literacy as a continuous measure) and outcomes in univariate models

		Patient attributes															Processes of care					Clinical parameters													Lab measures													Clinical outcomes		
	Study	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 preparaedness	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 *et al.* [20]										♦																																							
	Blandon *et al.* [22]																									♦a																								
	Dageforde *et al.* [24]																																	o																
	Devraj *et al.* [15]											o																							♦	o														
	Kazley *et al.* [30]													♦																																				
	Nelson *et al.* [31]		♦	o																																														
	Puher *et al.* [33]							♦																																										
	Rao *et al.* [34]									o																	o																							
	Segal *et al.* [35]				o																																													
	Singla *et al.* [19]																o					♦													♦															
	Wright *et al.* [40]					♦																																												
	Wright-Nunes *et al.* [41]						♦								o																																			
	Wright-Nunes *et al.* [42]									o																																								
Dialysis	Adeseun *et al.* [31]																						o	♦	♦					o	o														o	o	o			
	Basu *et al.* [20]										♦																																							
	Cavanaugh *et al.* [16]																											o		o		♦					o	o	o	♦	o	o	o	o						♦
	Cavanaugh *et al.* [23]																											♦																						
	Dageforde *et al.* [24]																																	o																
	Foster *et al.* [25]															o																																		
	Green *et al.* [17]																	o	o	♦	o								♦								o		o	o	o	o		o						o
	Grubbs *et al.* [27]												o																																			o	♦	
	Jain *et al.* [28]																																o						o		o									
	Jang *et al.* [29]								o																																									
	Kazley *et al.* [30]													♦																																				
	Posodas *et al.* [32]																											o																						
	Shirsalkar *et al.* [36]					♦																											o																	
	Singh *et al.* [37]																											o											o	o	o			o						
	Vourakis *et al.* [38]																																							o	♦									
Transplant	Gordon and Wolf [26]																																		o															
	Kazley *et al.* [30]													♦																																				
	Weng *et al.* [39]	o																																																

Filled markers indicate statistically significant associations. Unfilled markers indicate non-significant associations. Shading of author name indicates cohort study.

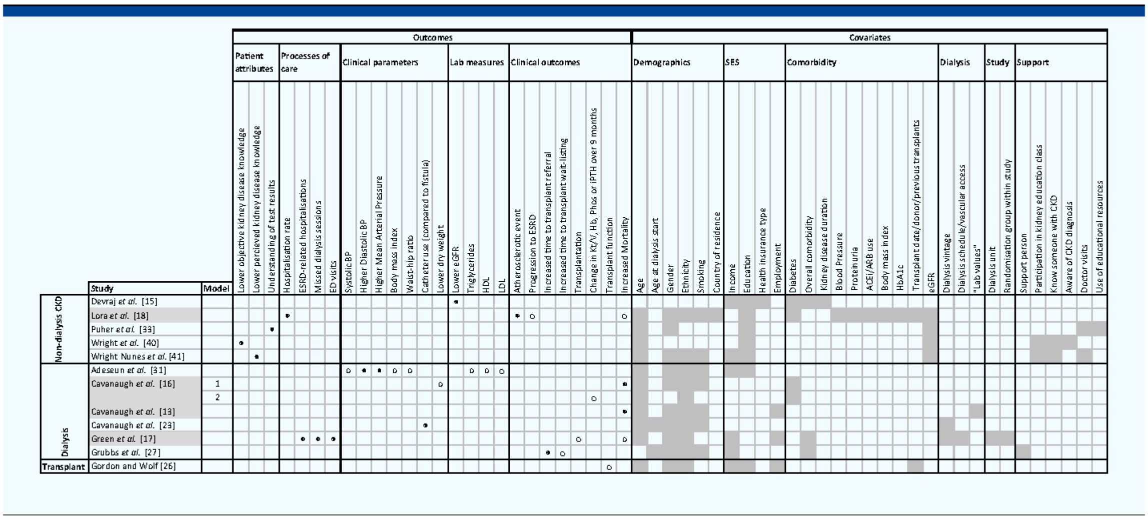
^{a}In a subgroup only (women with diabetes), not significant for other groups.

ED, emergency department; BP, blood pressure; IDWG, intra-dialytic weight gain; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[13, 16], although one study lacked adjustment for comorbidity and the other lacked adjustment for socio-economic status. A smaller cohort study with adjustment for both comorbidity and socio-economic status [17] 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 socio-economic variables (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 higher blood pressure among dialysis patients with lower health literacy [21]. There was no consensus from several studies on a relationship between limited health literacy and haemodialysis access [16, 17, 23, 32, 37]. 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 [30], 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 [27]. Kidney transplant recipients, especially recipients of living donor or pre-emptive transplants, have significantly higher health literacy than dialysis patients [33, 43] and other surgical patients [44], 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

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**



			Outcomes																										Covariates																														
			Patient attributes			Processes of care				Clinical parameters							Lab measures				Clinical outcomes								Demographics						SES				Comorbidity										Dialysis			Study		Support					
	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	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 *et al.* [15]																●																		▨	▨	▨		▨	▨	▨																		
	Lora *et al.* [18]					●															●	○						○	▨		▨	▨	▨	▨		▨			▨			▨	▨	▨	▨	▨	▨	▨											
	Puher *et al.* [33]				●																								▨		▨					▨												▨										▨	▨
	Wright *et al.* [40]		●																										▨							▨												▨							▨	▨	▨		
	Wright Nunes *et al.* [41]			●																									▨		▨	▨	▨		▨	▨												▨							▨	▨		▨	
Dialysis	Adeseun *et al.* [31]									○	●	●	○	○				○	○	○									▨		▨	▨	▨		▨	▨																							
	Cavanaugh *et al.* [16]	1														○												●	▨		▨	▨	▨						▨																				
		2																								○			▨			▨							▨																				
	Cavanaugh *et al.* [13]																											●	▨		▨	▨	▨					▨													▨								
	Cavanaugh *et al.* [23]														●														▨	▨	▨	▨	▨																▨										
	Green *et al.* [17]						●	●	●																○			○	▨		▨	▨			▨			▨		▨									▨	▨		▨	▨						
	Grubbs *et al.* [27]																						●	○						▨	▨	▨	▨		▨					▨														▨					
Transplant	Gordon and Wolf [26]																										○		▨		▨	▨			▨	▨		▨									▨												

Filled markers indicate statistically significant associations. Unfilled markers indicate non-significant associations. Shading of author name indicates cohort study.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; ED, emergency department; Hb, haemoglobin; HDL, high-density lipoprotein; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein; Phos, phosphate.

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 socio-economic status and comorbidity, both of which are strongly associated with limited health literacy [12, 43].

In other healthcare settings, systematic reviews of health literacy and health outcomes report associations between limited health literacy and reduced medical knowledge [45], reduced use of preventative medicine, reduced ability to interpret written information or manage medications, increased risk of hospitalization including emergency department use [46], lower health status and increased mortality [3, 47]. The overall lack of research into the causal effect of limited health literacy on health outcomes is noted [3, 44]. 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 [48].

This review benefits from a broad search strategy including updated health literacy terms, and an extensive search of conference abstracts that 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 socio-economic status, patients with limited health literacy in USA are more likely to be uninsured, with associated reduced access to care—this association could confound results. Secondly, 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. Thirdly, there was wide variation in the age, gender and ethnicity of participants, making comparison between studies difficult. Fourthly, although we obtained additional information by contact with authors, the detail available was limited because 16 of 29 studies were reported only as conference abstracts. However, inclusion of conference abstracts in the review demonstrates the volume of unpublished health literacy research that exists (with negative studies possibly subject to publication bias), and allowed us to report preliminary results from large cohort studies whose publication is awaited [13, 18]. Fifthly, differences between health literacy measures limits between-study comparability. The health literacy measures used included comprehension assessments such as REALM (Rapid Estimate of Adult Health Literacy in Medicine), STOFHLA (Short Test of Functional Health Literature in Adults) and Newest Vital Sign (NVS), which directly assess individuals' understanding, and screening tools such as the Brief Health Literacy Screen (BHLS), which record patient-reported understanding. Although screening measures have been validated against comprehension assessments [49], 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. Lastly, although this review was registered with the international prospective register of systematic reviews, data collection had already begun at the time of registration.

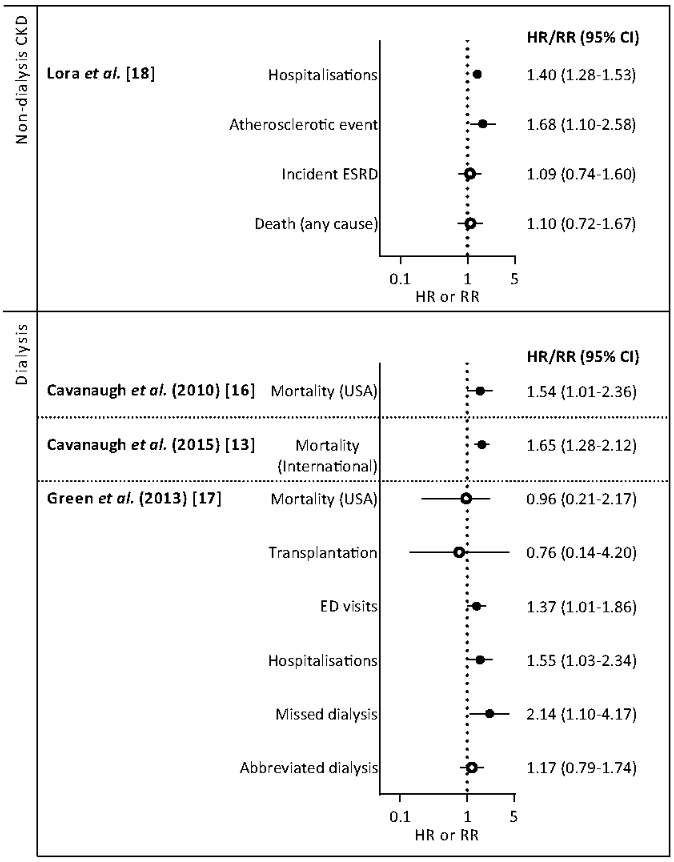


FIGURE 2: Summary of effect sizes for associations with limited (versus adequate) health literacy in cohort studies. Covariates included in multivariate models are shown in Table 5. Cross-sectional results from baseline data in cohort studies not shown (shown in Tables 4 and 5). Results from Singla *et al.* (2016) [19] (a negative association between limited health literacy and hospitalizations, and a positive association between limited health literacy and dialysis initiation) are not shown because measures of effect were not available. ED, emergency department.

Around 25% of people with CKD have limited health literacy, which disproportionally affects those with low socio-economic 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 socio-economic status and outcomes, health literacy may be a target for interventions to reduce socio-economic 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 [50]. 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 [51], 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, socio-economic status and comorbidity should be considered, and mediation pathways examined [52]. 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 randomized 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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AUTHORS' CONTRIBUTIONS

D.M.T. performed the literature searches, compiled the tables and figures and was the primary author of the article. D.M.T. and S.F. screened the results of literature searches, identified studies for inclusion and assessed study quality. R.R. and P.R. were supervising authors. C.D., G.C.O. and C.T. edited the manuscript further.

CONFLICT OF INTEREST STATEMENT

G.C.O. received royalties from book authorship (Wiley), unrelated to this manuscript. P.R. received grant support from Pfizer 2012–14 for an MRSA study, unrelated to this manuscript. The other authors had nothing to declare. The results presented in this article have not been published previously in whole or in part.

SUPPLEMENTARY DATA

Supplementary data are available online at ndt online.

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clinical investigation

Limited health literacy in advanced kidney disease

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Limited health literacy may reduce the ability of patients with advanced kidney disease to understand their disease and treatment and take part in shared decision making. In dialysis and transplant patients, limited health literacy has been associated with low socioeconomic status, comorbidity, and mortality. Here, we investigated the prevalence and associations of limited health literacy using data from the United Kingdom–wide Access to Transplantation and Transplant Outcome Measures (ATTOM) program. Incident dialysis, incident transplant, and transplant wait-listed patients ages 18 to 75 were recruited from 2011 to 2013 and data were collected from patient questionnaires and case notes. A score >2 in the Single-Item Literacy Screener was used to define limited health literacy. Univariate and multivariate analyses were performed to identify patient factors associated with limited health literacy. We studied 6842 patients, 2621 were incident dialysis, 1959 were wait-listed, and 2262 were incident transplant. Limited health literacy prevalence was 20%, 15%, and 12% in each group, respectively. Limited health literacy was independently associated with low socioeconomic status, poor English fluency, and comorbidity. However, transplant wait-listing, preemptive transplantation, and live-donor transplantation were associated with increasing health literacy.

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KEYWORDS: dialysis; health care disparities; health literacy; kidney transplantation; social class

The term "health literacy" describes patients' ability to access, understand, interpret, and use health-related information to manage and improve health.[1] As a concept, health literacy is distinct from, but influenced by general literacy and numeracy.[2] Limited health literacy is associated with difficulty managing medications, poorer overall health, increased mortality, and less efficient use of health services in the general populations.[3] The existence of a "social gradient" of health literacy,[4] whereby those with low socioeconomic status also have low health literacy, may promote health inequity. Poor health literacy also appears to mediate the negative effect of nonwhite ethnicity on patient activation, a separate construct that enables effective decision making.[5,6] In this way, health literacy differences may perpetuate the effect of ethnicity on access to health care services.

Patients with advanced kidney disease, who may be receiving dialysis, preparing for transplantation, or living with a kidney transplant are required to cope with complex medication regimens, dietary changes, the limited flexibility of dialysis treatment schedules and frequent outpatient appointments. These activities require health navigation skills, the ability to gain health knowledge, motivation, and problem-solving abilities, all of which are components of personal health literacy.[7] Shared decision-making strategies and the promotion of self-care can improve patient satisfaction and health in kidney disease,[8] and this is reflected in national health care policies.[9,10] However, adequate health literacy is a prerequisite for patient engagement with shared decision making.[11,12]

Interventions that attempt to improve health literacy or compensate for poor health literacy have become a priority in kidney disease care,[13,14] although such strategies could be more effective if more were known about the associations of limited health literacy and the mechanisms of any effect on outcomes. A recent systematic review of the effects of health literacy on health outcomes included no studies of kidney disease patients and identified the need for large-sample, nationally representative data.[3] In general populations, lower literacy or numeracy is associated with the presence of a long-term health conditions[15] and with mortality in older people.[16]

In the USA, the prevalence of limited health literacy and its associations have been described in chronic kidney disease patients,[17] although there is marked heterogeneity in the

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reported prevalence of limited health literacy, likely to be related to relatively small sample size, the use of different health literacy measures, and the varying characteristics of the study participants. Poorer health literacy has been associated with mortality and reduced likelihood of referral for transplantation in US hemodialysis patients, and recipients of live-donor kidney transplants have been found to be more health literate than those receiving deceased-donor transplants.[18–21] In UK patients with kidney disease, there has been little work undertaken to identify the scale of the health literacy problem and its associations.

In this large UK-wide study of over 6800 patients, we aimed to determine the prevalence of limited health literacy and its associations with demographics, comorbidity, and socioeconomic status in patients at 3 different stages of treatment: at initiation of dialysis, while on the kidney transplant waiting list, and at the point of kidney transplantation. We also considered the potential implications for patients' progress toward transplantation.

RESULTS

A total of 6842 patients were recruited: 2621 incident dialysis patients, 1959 wait-listed patients, and 2262 incident transplant patients, including 469 patients who contributed data to >1 group. The process of patient inclusion is shown in Figure 1.

Prevalence of limited health literacy

Health literacy was measured using the Single-Item Literacy Screener (SILS): "How often do you need to have someone help you when you read instructions, pamphlets or other written material from your doctor or pharmacy?" Options were 1—Never, 2—Rarely, 3—Sometimes, 4—Often, and 5—Always. Responses "Sometimes," "Often," and "Always" were selected to represent limited health literacy. This decision was informed by work where the SILS was validated against the Short Test of Functional Health Literacy in Adults (S-TOFHLA), a 36-item health literacy assessment tool.[22,23] Responses to the SILS in each group are shown in Figure 2. The prevalence of limited health literacy was 20% in the incident dialysis group, 15% in the wait-listed group, and 12% in the incident transplant group. The distribution of individual SILS scores and the prevalence of limited health literacy differed significantly between groups ($P < 0.001$). Figure 3 shows the patient pathways to transplantation and the prevalence of limited health literacy among patients in each group and subgroup.

Associations with limited health literacy

Table 1 shows the patient characteristics and univariate analyses comparing patients with adequate and limited health literacy within each group. Figure 4 shows the results of fully adjusted logistic regression models identifying patient factors associated with limited health literacy.

In the incident dialysis group, fully adjusted models showed that limited health literacy was significantly associated with younger age, poorer English fluency, higher comorbidity, depression, psychosis, lower educational level, unemployment, or long-term disability (when compared with full-time employment), the absence of car or home ownership and having >2 children. Current smoking was associated with reduced odds of limited health literacy.

Similar associations were found in the wait-listed group, although stronger associations between limited health literacy and unemployment or long-term disability were detected. Depression, absence of home ownership, and number of children were not significantly associated with limited health literacy in the wait-listed group.

The incident transplant group showed similar patterns of association, except that patients of black ethnicity were significantly less likely to have limited health literacy than those of white ethnicity. However this association relates to a small number of observations: only 8 black patients in this group had limited health literacy.

Patients of Asian ethnicity had significantly higher odds of limited health literacy than did white patients, but these differences were not significant after adjustment for English fluency (see Supplementary Results and Supplementary Table S1). Although lower educational level was associated with limited health literacy in all 3 groups, education did not predict health literacy entirely: between 3% and 10% of patients with university-level qualifications had limited health literacy.

After multiple imputations to account for missing data, the prevalence of limited health literacy in each group remained the same. Pooled estimates of logistic regression models from 20 imputed datasets in each group showed no major differences when compared with the models including complete cases only. Results from these models are shown in the Supplementary Results and Supplementary Table S2.

Comparison of patient groups

Figure 3 shows the patient groups and subgroups and relative prevalence of limited health literacy. Tables 2 and 3 show univariate and multivariate analyses comparing the prevalence of limited health literacy between patient subgroups. Incident dialysis patients had a significantly higher prevalence of limited health literacy than did wait-listed patients on dialysis (Figure 3, marker A). This difference was statistically significant until adjustment for socioeconomic status, and adding adjustment for comorbidity further reduces the effect of group on the likelihood of limited health literacy.

By univariate analysis, there were no significant differences in limited health literacy prevalence between patients wait-listed on dialysis and recipients who underwent deceased-donor transplantation, excluding patients transplanted preemptively (marker B in Figure 3) or between patients wait-listed preemptively and those who received a deceased-donor preemptive transplant (marker C in Figure 3).

Preemptive live-donor transplant recipients had a significantly lower prevalence of limited health literacy than

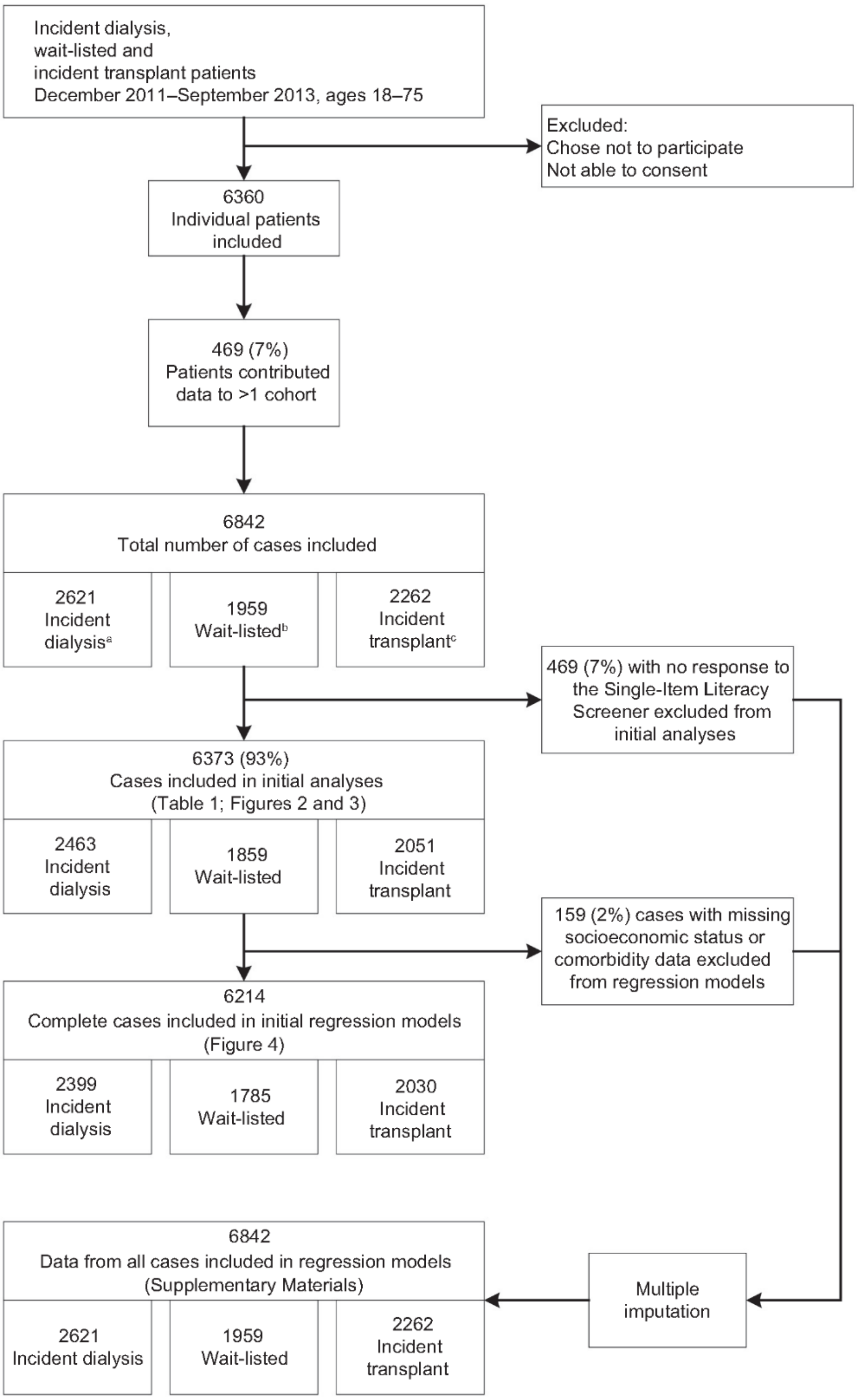

Figure 1 | Patient inclusion process. [a]The proportion of patients recruited to the incident dialysis group is difficult to quantify because of differing start and end times of the research nursing contracts at each center, although a comparison between patients recruited to Access to Transplantation and Transplant Outcome Measures (ATTOM) during 2012 and data from the UK Renal Registry showed that >50% of UK incident dialysis patients under 75 years were enrolled to ATTOM during that year. [b]Includes 74% of patients transplanted in the UK during the study period. [c]Includes 91% of wait-listed patients who were approached for inclusion.

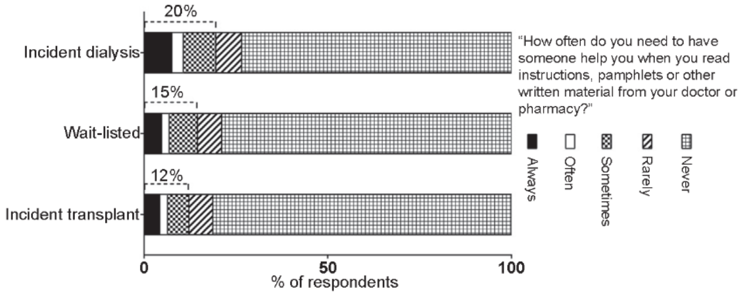

Figure 2 | Responses to the Single-Item Literacy Screener by patient group. Percentages indicate the prevalence of limited health literacy in each group. The distribution of responses was significantly different between groups by chi-square test, $P < 0.001$.

live-donor recipients transplanted after starting dialysis. In multivariate models, adding adjustment for socioeconomic status had the largest effect on the magnitude of this difference. Live-donor transplant recipients had a significantly lower prevalence of limited health literacy than deceased-donor recipients did, until adjustment for socioeconomic status, in both preemptively transplanted patients and those transplanted after starting dialysis.

DISCUSSION

This is the first UK-wide research to examine the prevalence and associations of limited health literacy among patients with kidney disease and to compare prevalence between dialysis and transplanted groups in a single population. This large nationwide study of >6800 patients ages <75 from every renal unit in the UK showed that limited health literacy was common with a prevalence of limited health literacy of

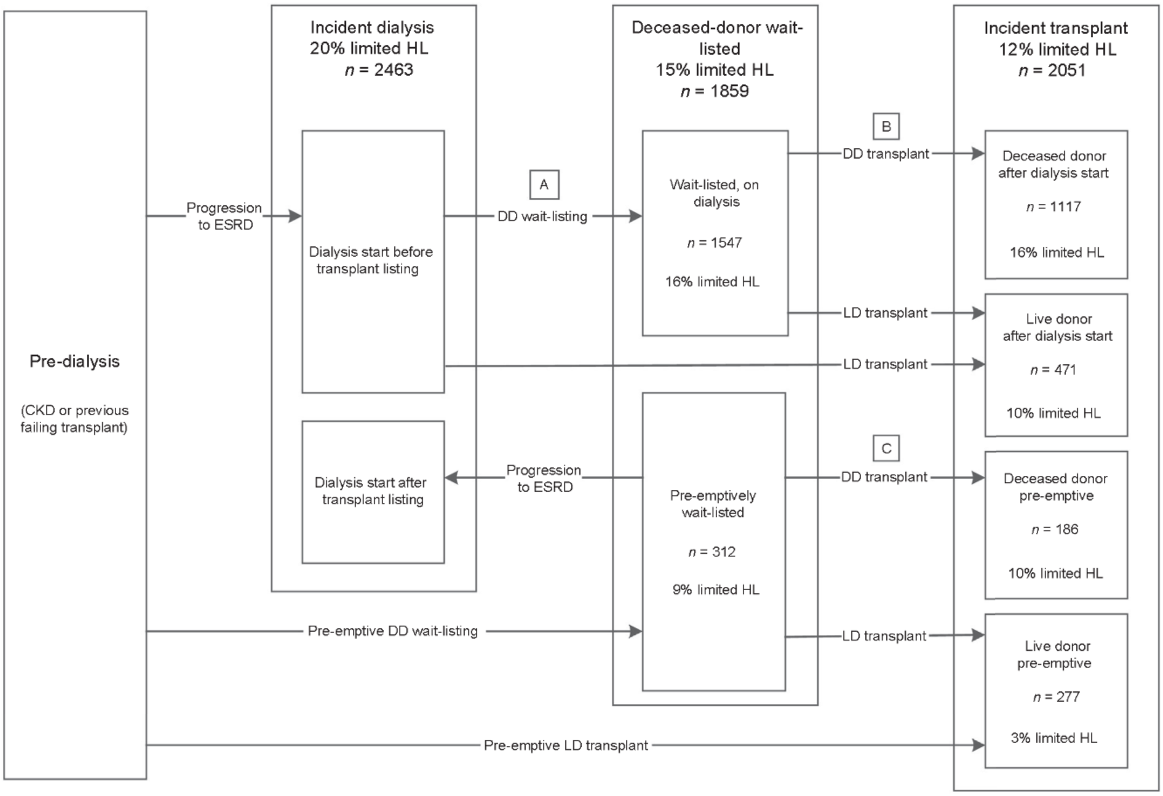

Figure 3 | Patient pathways to transplantation and the point prevalence of limited health literacy among patients at each stage. Markers A to C indicate points in patient pathways influenced by the deceased donor (DD) transplant wait-listing and selection process. Although DD wait-listing is not necessary to achieve a live-donor (LD) transplant, most LD recipients would have been added to the waiting list at the time of transplantation. CKD, chronic kidney disease; ESRD, end-stage renal disease; HL, health literacy.

Table 1 | Patient characteristics by group and health literacy status

	Incident dialysis, *n* = 2463			Wait listed, *n* = 1859			Incident transplant, *n* = 2051		
	Heath literacy			Heath literacy			Heath literacy		
	Adequate	Limited	*P*	Adequate	Limited	*P*	Adequate	Limited	*P*
	1982 (80%)	481 (20%)		1589 (85%)	270 (15%)		1801 (88%)	250 (12%)	
Male	1294 (65)	311 (65)	0.795	917 (58)	160 (59)	0.633	1128 (63)	152 (61)	0.575
Median age (IQR)	58 (47–, 67)	58 (47, 66)	0.636	51 (41, 61)	48 (39, 58)	**0.008**	50 (39, 60)	49.5 (41, 58)	0.812
Ethnicity									
White	1661 (84)	322 (67)	**<0.001**	1223 (77)	166 (61)	**<0.001**	1510 (84)	178 (71)	**<0.001**
Asian	140 (7)	107 (22)		153 (10)	68 (25)		137 (8)	52 (21)	
Black	140 (7)	39 (8)		173 (11)	26 (9)		118 (7)	8 (3)	
Chinese	15 (1)	6 (1)		20 (1)	7 (3)		11 (1)	8 (3)	
Mixed race	25 (1)	7 (1)		19 (1)	3 (1)		24 (1)	4 (1)	
Language									
English first language	1800 (91)	338 (70)	**<0.001**	1390 (88)	168 (62)	**<0.001**	1647 (92)	167 (67)	**<0.001**
Other first language, self-reported English fluency									
Good	114 (6)	21 (4)		144 (9)	16 (6)		103 (6)	10 (4)	
Moderate	54 (3)	58 (12)		45 (3)	39 (14)		39 (2)	31 (12)	
Poor or no English	13 (1)	64 (13)		7 (0.4)	47 (17)		11 (1)	42 (17)	
Modified Charlson Comorbidity Index									
0	913 (46)	124 (26)	**<0.001**	1108 (70)	152 (56)	**<0.001**	1281 (71)	130 (52)	**<0.001**
1–2	692 (35)	230 (48)		400 (25)	95 (35)		422 (23)	99 (40)	
3–4	240 (12)	89 (19)		60 (4)	16 (6)		76 (4)	20 (8)	
>4	137 (7)	38 (8)		21 (1)	7 (3)		22 (1)	1 (0.4)	
Individual comorbidities									
Myocardial infarction	185 (9)	58 (12)	0.072	65 (4)	15 (6)	0.273	55 (3)	9 (4)	0.642
Heart failure	120 (6)	35 (7)	0.301	34 (2)	10 (4)	0.116	34 (2)	6 (2)	0.587
Peripheral vascular disease	159 (8)	58 (12)	**0.004**	55 (3)	12 (5)	0.413	50 (3)	15 (6)	**0.007**
Cerebrovascular disease	142 (7)	62 (13)	**<0.001**	76 (5)	20 (8)	0.070	75 (4)	22 (9)	**0.001**
Dementia	4 (0.2)	0	1.0	3 (0.2)	0	1.0	1 (0.06)	0	1.0
Respiratory disease	214 (11)	59 (13)	0.317	99 (6)	16 (6)	0.870	127 (7)	14 (6)	0.391
Diabetes	690 (35)	301 (64)	**<0.001**	242 (15)	72 (27)	**<0.001**	293 (16)	88 (35)	**<0.001**
Diabetic nephropathy	417 (21)	216 (46)	**<0.001**	156 (10)	59 (22)	**<0.001**	210 (12)	75 (30)	**<0.001**
Cirrhotic liver disease	23 (1)	4 (1)	0.806	2 (0.1)	0 (0)	1.0	10 (1)	1 (0.4)	1.0
Leukemia	5 (0.25)	1 (0.2)	1.0	2 (0.1)	1 (0.4)	0.376	2 (0.1)	0	1.0
Lymphoma	20 (1)	2 (0.4)	0.286	11 (0.7)	2 (0.7)	1.0	9 (0.5)	0	0.611
Psychosis	4 (0.2)	9 (2)	**<0.001**	2 (0.1)	8 (3)	**<0.001**	2 (0.1)	5 (2)	**<0.001**
Depression	113 (6)	48 (10)	**0.001**	89 (6)	18 (7)	0.5	74 (4)	15 (6)	0.118
Malignancy	263 (13)	41 (9)	**0.006**	110 (7)	11 (4)	0.084	109 (6)	11 (4)	0.294
Primary renal disease									
Diabetes	417 (21)	216 (45)	**<0.001**	156 (10)	59 (22)	**<0.001**	210 (12)	75 (30)	**<0.001**
Glomerulonephritis or SLE	389 (20)	63 (13)		450 (28)	42 (16)		522 (29)	46 (18)	
Polycystic kidney disease	185 (9)	23 (5)		272 (17)	36 (13)		286 (16)	25 (10)	
Pyelonephritis or TIN	144 (7)	23 (5)		179 (11)	32 (12)		204 (11)	19 (8)	
Hypertensive, renovascular or ischemic nephropathy	188 (9)	35 (7)		104 (7)	17 (6)		113 (6)	18 (7)	
Other	659 (33)	121 (25)		428 (27)	84 (31)		466 (26)	67 (27)	
Smoking									
Never smoked	1103 (56)	282 (59)	0.481	1005 (63)	175 (65)	0.773	1187 (66)	164 (66)	0.670
Ex-smoker	567 (29)	126 (26)		238 (15)	36 (13)		482 (27)	64 (26)	
Current smoker	310 (16)	73 (15)		345 (22)	59 (22)		131 (7)	22 (9)	
Median BMI (IQR)	27 (23, 32)	27 (24, 33)	**0.022**	26 (23, 29)	26 (23, 30)	0.210	26 (23, 29)	25 (23, 29)	0.606
Highest educational level									
None	568 (30)	245 (51)	**<0.001**	331 (21)	125 (47)	**<0.001**	311 (17)	112 (45)	**<0.001**
High-school level	858 (43)	156 (33)		805 (51)	95 (35)		925 (52)	96 (39)	
University level	355 (18)	39 (8)		340 (22)	25 (9)		436 (24)	14 (6)	
Other	193 (10)	40 (8)		104 (7)	23 (9)		122 (7)	26 (10)	
Car owner	1479 (75)	272 (57)	**<0.001**	1268 (80)	174 (65)	**<0.001**	1543 (86)	178 (71)	**<0.001**
Homeowner	1135 (58)	191 (40)	**<0.001**	934 (59)	106 (39)	**<0.001**	1163 (65)	125 (50)	**<0.001**
Marital status									
Married	1101 (56)	244 (51)	**0.001**	801 (51)	128 (48)	0.770	957 (53)	127 (51)	0.595
Living with partner	135 (7)	22 (5)		131 (8)	20 (7)		162 (9)	17 (7)	
Divorced or separated	240 (12)	85 (18)		226 (14)	38 (14)		190 (11)	32 (13)	
Widowed	108 (5)	39 (8)		55 (3)	10 (4)		52 (3)	7 (3)	
Single	388 (20)	89 (19)		369 (23)	72 (27)		435 (24)	65 (26)	

(*Continued on next page*)

Table 1 | (Continued) Patient characteristics by group and health literacy status

	Incident dialysis, $n = 2463$			Wait listed, $n = 1859$			Incident transplant, $n = 2051$		
	Heath literacy			Heath literacy			Heath literacy		
	Adequate	Limited	*P*	Adequate	Limited	*P*	Adequate	Limited	*P*
Employment									
Full time	293 (15)	15 (3)	**<0.001**	399 (25)	15 (6)	**<0.001**	509 (28)	22 (9)	**<0.001**
Part time	163 (8)	18 (4)		206 (13)	23 (9)		192 (11)	15 (6)	
Unemployed	145 (7)	35 (7)		125 (8)	36 (13)		140 (8)	27 (11)	
Long-term sickness/disability	542 (27)	228 (48)		395 (25)	140 (52)		455 (25)	121 (49)	
Student	19 (1)	1 (0.2)		28 (2)	0		38 (2)	2 (1)	
Retired	741 (38)	166 (35)		363 (23)	41 (15)		370 (21)	39 (16)	
Not working (other)	28 (1)	5 (1)		23 (1)	6 (2)		50 (3)	7 (3)	
Looking after home	44 (2)	12 (3)		43 (3)	8 (3)		43 (2)	15 (6)	
Number of children									
0	1575 (80)	360 (75)	**0.001**	1165 (74)	189 (71)	**0.016**	1319 (73)	188 (75)	0.153
1–2	345 (17)	91 (19)		370 (23)	60 (22)		407 (23)	47 (19)	
>2	53 (3)	29 (6)		50 (3)	18 (7)		71 (4)	15 (6)	

BMI, body mass index; IQR, interquartile range; SLE, systemic lupus erythematosus; TIN, tubulointerstitial nephritis.
Results displayed as frequency (percentage) unless otherwise specified. *P* values indicate the results of univariate analyses comparing those with adequate versus limited health literacy. Bold *P* values are statistically significant. Group percentages may not exactly equal 100% because of rounding.

20% among incident dialysis patients, 15% among transplant wait-listed patients, and 12% among incident transplant patients. It was associated with lower employment, lower educational level, absence of car and home ownership, lower English fluency, and higher comorbidity.

The prevalence of limited health literacy reduced during the process of selection for transplantation. The most health-literate groups were live-donor transplant recipients and patients listed or transplanted preemptively, and this health literacy difference appears to be related to higher socioeconomic status and lower comorbidity. When live-donor and preemptively transplanted patients are excluded, significant differences in health literacy remain between incident dialysis and wait-listed patients, until adjustment for socioeconomic status and comorbidity.

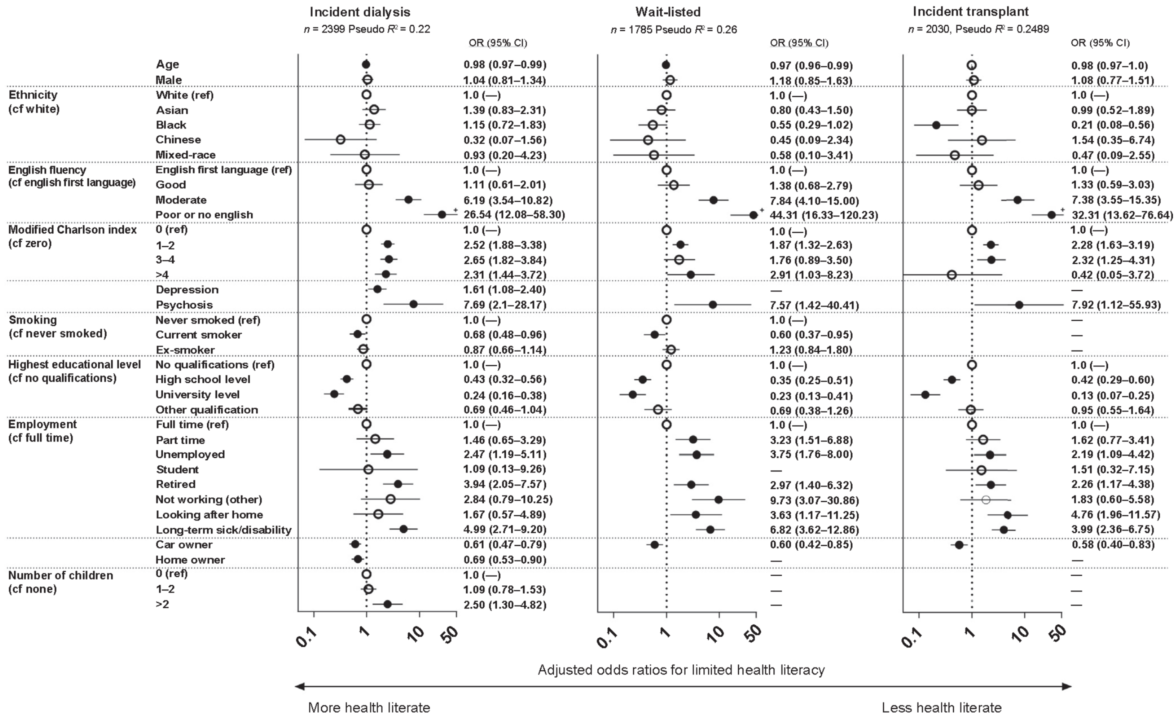

Figure 4 | Results of multivariate logistic regression models for the odds of limited health literacy by patient group. Markers are shown for variables included in each model. Filled markers indicate statistical significance ($P < 0.05$). Error bars indicate 95% confidence intervals (CIs). "+" indicates upper bound of confidence interval is >50. Absent markers indicate variables that did not reach statistical significance and were excluded from the model. There were no students with limited health literacy in the wait-listed group. OR, odds ratio.

Table 2 | Comparison of limited health literacy prevalence in patient groups, univariate analyses

		Unadjusted odds ratio for limited health literacy (95% CI)	*P*
A: Wait-listed on dialysis compared with incident dialysis[a]	Incident dialysis (ref)	1	0.003
	Wait-listed, on dialysis	0.77 (0.64–0.92)	
B: Incident deceased donor transplant compared with deceased donor wait-listed[a]	Wait listed, on dialysis (ref)	1	0.677
	Deceased-donor transplant after dialysis start	0.95 (0.75–1.20)	
C: Preemptive deceased-donor transplant compared with preemptively wait-listed[a]	Preemptively wait-listed (ref)	1	0.561
	Preemptive deceased-donor transplant	1.18 (0.68–2.06)	
Preemptive listing or transplant compared with listing or transplant after dialysis start	Wait listed, on dialysis (ref)	1	0.001
	Preemptively wait-listed	0.51 (0.32–0.78)	
	Deceased-donor transplant after dialysis start (ref)	1	0.057
	Preemptive deceased donor transplant	0.62 (0.35–1.03)	
	Live donor transplant after dialysis start (ref)	1	0.001
	Preemptive live-donor transplant	0.30 (0.13–0.62)	
Live donor transplant compared with deceased donor	Deceased donor transplant after dialysis start (ref)	1	0.005
	Live-donor transplant after dialysis start	0.61 (0.43–0.87)	
	Deceased-donor preemptive transplant (ref)	1	0.002
	Live-donor preemptive transplant	0.30 (0.12–0.71)	

ref, reference.

A to C refer to markers A to C in patient pathways indicated in Figure 3. Groups with statistically significant differences by univariate analysis are included in multivariate analyses in Table 3.

[a] Excluding patients recruited into >1 group.

Patients of Asian ethnicity were more likely to have limited health literacy before adjustment for English fluency. We also found that transplanted patients of black ethnicity had significantly higher health literacy than transplanted patients of white ethnicity did. This contrasts with data from the USA, where black ethnicity is strongly associated with limited health literacy, even in transplanted patients.[18,24,25] This intriguing finding, based on a small number of observations, warrants further prospective investigation in our future work.

The prevalence of limited health literacy reported here is similar to values published previously: 16% to 32% in dialysis patients[18–20,24,26] and 2.4% to 14% in transplanted patients.[21,25,27] The significant heterogeneity of previous measurements reflects the smaller sample size in many studies, potential for selection bias resulting from the selection methods used, heterogeneity of patient characteristics, and the use of different health literacy measures. Live-donor transplant recipients have been shown elsewhere to have higher health literacy,[25] although higher health literacy among patients wait-listed or transplanted preemptively has not been reported previously.

Our study confirms associations among limited health literacy, low socioeconomic status, and increased comorbidity in patients with advanced kidney disease.[18,20,24,25] The explanation for these associations is likely to be complex. Theoretical models of disease complexity describe the competing factors that affect patients' success in managing chronic disease in terms of "burden of disease,"[28] and "patient capacity" to cope.[29] Capacity is influenced by several factors including health literacy, financial and social support, and functional effects of illness such as mobility and cognition. Limited health literacy therefore affects a group of patients with both impaired capacity and higher burden of disease. This imbalance between capacity and disease burden is likely to impair patients' success in navigating health care services and may impede access to kidney transplantation. We detected higher health literacy in wait-listed patients than in incident dialysis patients, in live-donor transplant recipients than in deceased-donor transplant recipients, and in preemptively listed or transplanted patients than in those listed or transplanted after starting dialysis. In part, these differences may be explained by the exclusion of comorbid patients on the basis of poor fitness for transplantation, who may have lower health literacy as a result of cognitive impairment or from shared risk factors. However, socioeconomic status also appeared important in explaining the health literacy gap between transplanted patients and those on dialysis. Lower socioeconomic status[30] and limited health literacy[20] are known to be associated with reduced likelihood of transplant listing, and we hypothesize that limited health literacy may act as a mediating factor in the effect of low socioeconomic status on patient outcomes including access to transplantation. However, there is an established strong association between multimorbidity and low socioeconomic status[31] that could lead to residual confounding after adjustment for modified Charlson index and augment the apparent associations among socioeconomic status, health literacy, and access to transplantation.

Our study benefits from nationwide coverage and the use of a simple, validated health literacy measure to report on a large number of patients. We approached patients from all centers nationwide, reducing the risk of selection bias. Our sample of patients was broadly representative of the population,[32] though the number of peritoneal dialysis patients was underrepresented in the incident dialysis group, which would be expected to result in an overestimate of the true prevalence of limited health literacy among incident dialysis patients. The granularity of our socioeconomic status data has allowed us to identify associations between specific markers of poor socioeconomic status and health literacy and to differentiate between the effects of deprivation and the effect of educational level. We have also been able to adjust for an extensive list of comorbidities.

Table 3 | Sequentially fitted logistic regression models reporting odds ratios for limited health literacy between patient groups

	Odds ratios for limited health literacy (95% CI)									
	Wait-listed on dialysis compared with incident dialysis[a]		Preemptively wait-listed compared with wait-listed on dialysis		Preemptive live-donor transplant compared with live-donor transplant after dialysis start		Live-donor transplant after dialysis start compared with deceased-donor transplant after dialysis start		Live-donor preemptive transplant compared with deceased-donor	
	n = 3698		*n* = 1783		*n* = 704		*n* = 1566		*n* = 373	
		P		*P*		*P*		*P*		*P*
Model 1 Age, sex	0.74 (0.62–0.89)	0.001	0.50 (0.33–0.77)	0.002	0.32 (0.15–0.67)	0.002	0.57 (0.40–0.82)	0.002	0.34 (0.15–0.78)	0.011
Model 2a (ethnicity, language) As model 1 plus ethnicity and language	0.71 (0.58–0.86)	0.001	0.48 (0.30–0.77)	0.002	0.35 (0.16–0.77)	0.009	0.55 (0.38–0.81)	0.002	0.33 (0.14–0.82)	0.016
Model 2b (SES) As model 1 plus employment, car and home ownership, and education	0.84 (0.69–1.01)	0.070	0.81 (0.51–1.28)	0.368	0.46 (0.21–1.00)	0.049	0.72 (0.49–1.04)	0.084	0.47 (1.88–1.15)	0.097
Model 3 (ethnicity, language, SES) As model 1 plus factors in models 2a and 2b	0.79 (0.64–0.97)	0.027	0.75 (0.46–1.25)	0.272	0.55 (0.24–1.23)	0.146	0.69 (0.46–1.03)	0.068	0.53 (0.20–1.42)	0.205
Model 4 (comorbidity) As model 3 plus modified Charlson index, smoking, and psychosis	0.92 (0.74–1.14)	0.439	0.79 (0.48–1.31)	0.355	0.55 (0.25–1.27)	0.163	0.78 (0.52–1.17)	0.225	0.53 (0.20–1.45)	0.218

CI, confidence interval; SES, socioeconomic status

[a] Excluding patients recruited into both incident dialysis and wait-listed groups.

Our study has limitations. First, we recognize the limitations of the SILS. As a complex, multifaceted construct, no measure can capture all elements of individual health literacy, although comprehension-based measures do attempt to assess directly different health literacy elements, which cannot be addressed by a single question. For example, the SILS does not directly measure numeracy skills, which are independently associated with the prevalence of chronic diseases.[15] The SILS has been validated against other health literacy measures. In a primary care study of 999 adults with diabetes, the SILS was validated against S-TOFHLA (a 36-question health literacy evaluation tool). A threshold for limited health literacy of >2 (as in this study) detected limited health literacy with a sensitivity of 54% and specificity of 83%.[22] A study of 227 hemodialysis patients reported similar results: 39% sensitivity and 93% specificity.[23] Our results are therefore limited by the sensitivity of the SILS. More sensitive health literacy measures such as REALM (Rapid Estimate of Adult Literacy in Medicine) or S-TOFHLA may have addressed this limitation, but perhaps at the cost of longer surveys increasing the burden on patients, resulting in a reduced response rate. We therefore took a pragmatic approach: accept the limitations of the SILS in order to achieve a higher response rate. The result was a 93% response to the SILS. We accept that use of the SILS to define limited health literacy may overestimate or underestimate its true prevalence, although comparisons among the 3 treatment groups are likely to remain valid.

Second, we excluded patients over 75 years of age and those unable to give informed consent, so our results cannot necessarily be applied to elderly patients or those with significant cognitive impairment. Our results show that a large proportion of patients without overt cognitive impairment remain in need of help to understand health-related information.

Third, patients who were enrolled in >1 group were not reassessed for health literacy when reenrolled, so any improvement in health literacy during patients' progression toward transplantation could not be assessed. Finally, given the cross-sectional design, the influence of limited health literacy on individual patients' progress to transplantation cannot be directly evaluated. However, our data raise the possibility of inequity in the process of wait-listing for deceased-donor transplantation and access to live-donor transplantation, whereby differences in socioeconomic status and associated limited health literacy appear to reduce access to transplantation. We will investigate these processes further in future prospective analysis.

"Limited health literacy" refers to a level of understanding equivalent to US sixth-grade or below: that expected of a child under 12. We should recognize that patients identified as having limited health literacy represent only the most severely affected by a global problem: a gap between the complexity of the health information we provide and patients' understanding.[33] For many, current communication methods in nephrology practice may not be effective, as reported in qualitative studies where patients report wanting more information about their condition but feel bewildered by its complexity.[34] Our work suggests that poor health literacy disproportionately affects patients with lower socioeconomic status and higher comorbidity, and that poor understanding may perpetuate the effect of these factors on access to transplantation and outcomes by further reducing capacity to cope with disease and treatment.

When implementing strategies to improve patient outcomes by promoting self-management and shared decision making, we must recognize that limited health literacy is common in patients with kidney disease, and that patients with limited health literacy have coexisting barriers to success in the form of reduced capacity to cope and increased burden of illness.[35] These patients may benefit from enhanced communication methods and patient advocacy to help them navigate the pathway to transplantation. There may be a role for health literacy screening to identify patients most likely to benefit, using the SILS or other tools.[36] For those patients of Asian ethnicity whose first language is not English, language is the most important factor in reducing understanding, so increasing the availability of communication in patients' first languages may be the most effective way to improve engagement in the growing population of Asian patients with kidney disease in the UK.[37] Our future prospective analyses will aim to identify the effect of limited health literacy on patients' adherence to dialysis treatment, use of health care services, access to transplantation, and survival. Targeted interventions may be needed to reduce the effect of health literacy on inequity of treatment for patients with kidney disease.

MATERIALS AND METHODS

Design, setting, and participants

A cross-sectional study was undertaken using baseline data from the Access to Transplantation and Transplant Outcome Measures (ATTOM) program, which included a prospective, multicenter cohort study of patients with advanced kidney disease ages 18 to 75 years from all 72 renal units in the UK between December 2011 and September 2013. Patients were enrolled at 3 different stages in treatment: within 90 days of starting dialysis (incident dialysis), while on the transplant waiting-list (wait-listed), and within 90 days of transplantation (incident transplant). The wait-listed patients were selected as matched control subjects 1:1 to the incident transplant group, and data were collected within 90 days of their enrolment. Some patients transferred between groups during the study period, for instance, wait-listed patients who were transplanted. In this situation, patients were recruited again and added as a separate patient record, contributing data to >1 group. Recipients of simultaneous pancreas and kidney transplants were included. Detailed methods for the ATTOM program have been published separately.[32]

Analysis of patients recruited to ATTOM versus nonrecruited patients during 2012 showed that there were no significant differences in age, sex, or ethnicity after correction for missing ethnicity data in the UK Renal Registry record (data not shown).

Measures

Comorbidities were recorded from a structured review of case notes by a team of designated research nurses. Patients completed a questionnaire that elicited demographic information, individual-level markers of socioeconomic status, and responses to the SILS, a single-question measure of health literacy.[22] The questionnaire was self-completed except in cases of physical disability where help was given. The provision of non-English interpretation was provided if required. For patients who were included in >1 group, case notes were reviewed again to record any change in comorbidities, but the patient questionnaire was not repeated.

The outcome of interest was limited health literacy, defined by the response to the SILS.[22,23] The exposure variables of interest were demographics, comorbidities, and individual-level markers of socioeconomic status. To quantify comorbidity, we used a modified Charlson index based on an index validated in populations with end-stage renal disease.[38,39] Details of the score are provided in the Supplementary Results and Supplementary Table S3.

Statistical analysis

We aimed to test the null hypothesis that limited health literacy is independent of demographics, comorbidity, and socioeconomic status in patients within 90 days of dialysis initiation, while on the transplant waiting list, and within 90 days of transplantation. In descriptive statistics, continuous variables are described as median (interquartile range) and binary variables as frequency (percentage) unless otherwise specified. The prevalence of limited health literacy and associated factors were analyzed within each group. Univariate analyses were performed, using Mann-Whitney *U* tests for continuous variables and chi-squared or Fisher exact tests for binary variables as appropriate.

To examine the associations among patient-specific factors and health literacy, we fitted logistic regression models for each group, with limited health literacy as the dependent variable. Age (as a continuous variable), sex, and ethnicity were included as independent variables in all models. A backward-stepwise approach was used to select other variables for inclusion in the final model from those that we hypothesized to be associated with health literacy. These covariates were defined *a priori* and removed from the model if they failed to reach statistical significance ($P < 0.05$). During the model-building process, the effect of adding the English fluency term on the relationship between ethnicity and health literacy was examined in each group. Interaction terms for ethnicity/English fluency and ethnicity/car ownership and modified Charlson score/car ownership were added to each model but removed from final models as they failed to reach statistical significance.

A small proportion (5%–9%) of patients who agreed to participate in the ATTOM program did not complete all or part of the patient survey, and around 1% of patients had missing comorbidity data due to inability to access case notes. Initially, regression models included data from complete cases only, so 628 cases (9%) were excluded. Patients with missing data were found to be significantly more likely to have diabetes or be of nonwhite ethnicity. To investigate the effect of these missing data, we performed multiple imputation, using "imputation by chained equations" to produce 20 imputed datasets per group. These were used to fit regression models by the same backward-stepwise approach, using data from all cases. Full details of this analysis are in the Supplementary Results and Supplementary Tables S2, S4, and S5.

To compare the prevalence of limited health literacy between patients at different stages of treatment with adjustment for demographics, comorbidities, and socioeconomic status, wait-listed patients were subdivided into those wait-listed preemptively (before starting dialysis) and those already on dialysis at the time of wait-listing. Transplanted patients were subdivided by preemptive transplantation versus transplantation after dialysis start and live-donor versus deceased-donor status. The prevalence of limited health literacy in these subgroups was then compared by univariate analysis. Where significant differences in limited health literacy prevalence were found, further logistic regression models were fitted, with limited health literacy as the dependent variable and patient subgroup as an independent variable. Sequential adjustment for factors shown to be associated with limited health literacy in the individual group analyses was then performed. Cases with missing data were excluded from these models, and where a model compared the prevalence of limited health literacy between 2 groups, patients recruited to both groups were excluded from the model.

All hypothesis tests were 2-tailed. A P value of <0.05 was deemed statistically significant. All statistical analyses were performed using Stata 12.1 (StataCorp LP, College station, TX, USA).

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary Results.

Table S1. The effect of adding adjustment for English fluency on the odds of limited health literacy in patients of Asian ethnicity.

Table S2. Comparison of regression models using imputed data and models using data from complete cases only.

Table S3. Score weightings for modified Charlson index based on Hemmelgarn et al.[38]

Table S4. Proportion of missing data for each variable by patient group.

Table S5. Comparison of demographics and comorbidity between patients with complete data and those with missing data.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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