Limited health literacy is associated with reduced access to kidney transplantation

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Complete List of Authors:	Taylor, Dominic; Southmead Hospital, Richard Bright Renal Service; University of Southampton, Primary Care and Population Sciences Bradley, Andrew; Department of Surgery, Addenbrookes Hospital, Cambridge University Bradley, Clare; Royal Holloway, University of London, Health Psychology Research Unit Draper, Heather; University of Warwick Warwick Medical School Dudley, christopher; Southmead Hospital, Richard Bright Renal Unit Fogarty, Damian; Queen's University of Belfast, Fraser, Simon; University of Southampton, Academic Unit of Primary Care and Population Sciences Johnson, Rachel; NHS Blood and Transplant, Leydon, Geraldine; Southampton University, Primary Care and Population Sciences, Faculty of Medicine Metcalfe, Wendy; Royal Infirmary of Edinburgh, Renal Medicine Oniscu, Gabriel; Royal Infirmary of Edinburgh, Transplant Unit Robb, Matthew; NHS Blood and Transplant Organ Donation and Transplantation Directorate Tomson, Charles; Newcastle upon Tyne NHS Foundation Trust, Renal Medicine Watson, Chris; University of Cambridge, Surgery Ravanan, Rommel; Southmead Hospital, Richard Bright Renal Unit Roderick, Paul; university of southampton, public health and medical statistics group

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Title

Limited health literacy is associated with reduced access to kidney transplantation

Authors

Dominic M Taylor MD,[a b] J Andrew Bradley PhD,[c] Clare Bradley PhD,[d] Heather Draper PhD,[e] Christopher Dudley MD,[b] Damian Fogarty MD,[f] Simon Fraser MD,[a] Rachel Johnson MSc,[g] Geraldine M Leydon PhD,[a] Wendy Metcalfe MD,[h] Gabriel C Oniscu MD,[i] Matthew Robb PhD,[g] Charles Tomson MD,[j] Christopher J.E. Watson MA,[c] Rommel Ravanan MD,[b]* Paul Roderick MD[a]* on behalf of the ATTOM investigators

Affiliations

a Academic Unit of Primary Care and Population Sciences, University of Southampton, UK

b Richard Bright Renal Service, North Bristol NHS Trust, UK

c Department of Surgery, University of Cambridge, and NIHR Cambridge Biomedical Research Centre, UK

d Health Psychology Research Unit, Royal Holloway, University of London, UK

e Warwick Medical School, University of Warwick, UK

f Belfast Health and Social Care Trust, Belfast, UK

g NHS Blood and Transplant, Bristol, UK

h Scottish Renal Registry, UK

i Transplant Unit, Royal Infirmary of Edinburgh, UK

j Department of Renal Medicine, Freeman Hospital, Newcastle-upon Tyne, UK

* These supervising authors contributed equally.

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Corresponding Author

Dr Dominic Taylor, Richard Bright Renal Service, Southmead Hospital, Bristol, BS10 5NB, United Kingdom, dominic.taylor@nbt.nhs.uk

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Abstract

Limited health literacy is common in patients with chronic kidney disease (CKD), and has been variably associated with adverse clinical outcomes. The prevalence of limited health literacy is lower in kidney transplant recipients than in individuals starting dialysis, suggesting selection of patients with higher health literacy for transplantation. We investigated the relationship between limited health literacy and clinical outcomes, including access to kidney transplantation, in a prospective UK cohort study of 2,274 incident dialysis patients aged 18-75 years. Limited health literacy was defined by a validated Single Item Literacy Screener (SILS). Multivariable regression was used to test for association with outcomes after adjusting for age, sex, socioeconomic status (educational level and car ownership), ethnicity, first language, primary CKD diagnosis, and comorbidity. In fully-adjusted analyses, limited health literacy was not associated with mortality, late presentation to nephrology, dialysis modality, haemodialysis vascular access, or pre-emptive kidney transplant listing, but was associated with reduced likelihood of listing for a deceased-donor transplant (hazard ratio, HR 0.68; 95% CI 0.51-0.90), receiving a living-donor transplant (HR 0.41; 95% CI 0.19-0.88), or receiving a transplant from any donor type (HR 0.65; 95% CI 0.44-0.96). Limited health literacy is associated with reduced access to kidney transplantation, independent of patient demographics, socioeconomic status, and comorbidity. Interventions to ameliorate the effects of low health literacy may improve access to kidney transplantation.

Keywords: Health Literacy; Kidney transplantation; Socioeconomic Status; Chronic Kidney Disease; Dialysis.

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Introduction

Patients with advanced chronic kidney disease (CKD) who start dialysis are required to cope with the demands of a high-intensity treatment, often with a burden of increasing symptoms.[1] When medically appropriate, kidney transplantation offers superior clinical outcomes compared to dialysis,[2, 3] and leads to improvements in self-reported health.[4] Over 80% of UK transplanted patients receive dialysis prior to transplantation,[5] so are required to participate in investigations, discussions (including with potential living kidney donors) and shared decisions to prepare for transplantation at a time when their capacity to do so may be diminished.

Patients' capacity to cope with these communication challenges may be enhanced by adequate health literacy,[6] which can aid understanding, appraisal and use of health-related information, as distinct from general literacy, language fluency or patient activation.[7] 'Limited' health literacy (a below-adequate level defined by health literacy measures[8]) is common, affecting 20-25% of the dialysis population, but a significantly lower proportion of transplant recipients (14%), suggesting that patients with higher health literacy are more likely to be transplanted.[9, 10] Limited health literacy is associated with low socioeconomic status, so has been implicated as a mediator of socioeconomic inequity in health outcomes.[11] There is some evidence of independent associations between lower health literacy and adverse clinical events, increased healthcare use and mortality in CKD,[8] but a lack of larger, prospective studies evaluating the effects of lower health literacy on renal replacement therapy and kidney transplant pathways.[8]

We aimed to identify independent associations between health literacy and clinical outcomes including access to kidney transplantation in UK patients starting dialysis.

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Results

Figure 1 shows the processes of patient recruitment and data collection. In total, 2274 of 2432 patients eligible for inclusion responded to the Single Item Literacy Screener (SILS) health literacy question. Table 1 summarises patient demographics, clinical and socioeconomic characteristics, by limited vs adequate health literacy, and results of univariate analyses. Table 2 shows results of multivariable analyses.

Baseline characteristics

As in the baseline analysis of this group,[10] patients with limited health literacy were more likely to have higher levels of comorbidity and lower socioeconomic status, including a lower level of educational attainment and reduced likelihood of car ownership.

Presentation, dialysis modality, and haemodialysis vascular access

Limited health literacy was associated with reduced likelihood of late presentation to nephrology care, but not after adjustment for primary renal diagnosis and comorbidity (Odds Ratio, OR: 0.70; 95% CI: 0.39-1.27). A lower proportion of patients with limited health literacy had peritoneal dialysis as their first dialysis modality, but this difference was not significant in multivariable models (unadjusted OR for peritoneal dialysis 0.73; 95% CI: 0.52-1.03). Limited health literacy was not associated with haemodialysis catheter use (unadjusted OR: 1.07, 95% CI: 0.86-1.33).

Access to transplantation and mortality

There was no significant difference between patients with limited vs adequate health literacy in pre-emptive deceased-donor transplant listing in univariate or multivariable analyses (Table 1 and Table 2). Figure 2 shows the specification of time-to-event variables for transplantation and mortality. In univariate analyses, patients with limited health literacy had a significantly lower likelihood of transplant listing after starting dialysis, living-donor transplantation and transplantation from any donor type, but no difference in mortality (Table 2, Figure 3). In fully-adjusted models (Table 2),

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patients with limited health literacy had a reduced likelihood of listing for deceased-donor transplant (n=1833; Hazard ratio; HR: 0.68; 95% CI: 0.51-0.91), living-donor transplantation (n=2180; HR: 0.41; 95% CI: 0.21-0.80), and transplantation from any donor type (n=2178 HR: 0.65; 95% CI: 0.45-0.92).

There was no difference between patients with limited vs adequate health literacy in likelihood of deceased-donor transplantation after listing (Supplementary results 1). There were no significant violations of the proportional hazards assumptions. (Supplementary results 2). Including patients with lower English fluency (Supplementary results 3; Table S1, Table S2), using Townsend deprivation index in place of socioeconomic status markers as covariates in multivariable models (Supplementary results 4; Table S3), or removing adjustment for clustering by renal centre (Supplementary results 5; Table S4) did not change overall results.

For the three transplant outcomes, missing data affected 6-8% of cases, affected more Asian patients and those with diabetes as primary renal diagnosis, and largely related to missing SILS response. There was no difference in the significance of results when effect sizes were estimated after multiple imputation of missing data (Supplementary results 6; Tables S5, S6 and S7).

Supplementary information is available at Kidney International's website

Discussion

In this UK cohort study of 2274 patients starting dialysis, limited health literacy was independently associated with reduced access to deceased-donor transplant listing, transplantation from a living-donor or transplantation from any donor type. Health literacy was not shown to affect protocol-driven systems for offering deceased-donor kidneys after listing.[12] The effect of limited health literacy in reducing access to transplantation is therefore likely to relate to patients' preparation for deceased or living-donor transplantation. Health literacy was not independently associated with dialysis modality, haemodialysis vascular access, pre-emptive transplant listing or mortality. The

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pathway to deceased-donor transplant listing could not be captured in a single variable because patients were recruited when starting dialysis, so those listed pre-emptively were considered in a separate analysis to those listed after starting dialysis. The absence of a significant association with pre-emptive listing may relate to loss of statistical power.

Pathways to deceased-donor transplant listing and living-donor transplantation depend on adequate clinician-patient communication and understanding to enable effective shared decision-making. Patients with limited health literacy may have reduced understanding of CKD, its consequences,[8] and the benefits of transplantation. They may feel less able or comfortable speaking and asking questions during clinical interactions[6] let alone driving discussions about transplantation. Current shared decision-making resources may be unsuitable for patients with limited health literacy.[13] Limited health literacy is hypothesised to reduce patients' capacity to cope with the burden of chronic disease and its treatment,[1] and associations with low socioeconomic status and comorbidity[10, 11] may further impede effective care. Patients with limited health literacy may lack understanding, so be less likely to discuss transplantation with family and friends, while social support mechanisms (providing opportunities for discussion) may be reduced by low socioeconomic status. Patients may be over-burdened by the process of dialysis preparation, preferring a 'short-term focus':[14] deferring preparations for transplantation until established on dialysis. The associated reduction in time accrued on the transplant list may reduce the likelihood of transplantation.[12] The recruitment of living donors presents a specific communication challenge, as a potential recipient needs to engage a potential donor. Potential donors, most commonly family members, may also have lower health literacy and health contraindications because of shared social disadvantages.[11] Lastly, the process of preparing for a kidney transplant may invoke considerable psychological stress. Patients with lower health literacy, less able to rationalise and understand pathways to transplantation, may find this process more frightening, limiting their ability to engage with it.

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In studies from the USA, health literacy is inconsistently associated with transplantation, dialysis catheter use, healthcare service use including emergency department attendance, and mortality.[8] Low health literacy has strong associations with low socioeconomic status,[9, 10] and there are persistent socioeconomic disparities in CKD, its complications,[15, 16] and in access to kidney transplantation.[17, 18] As such, limited health literacy may lie on the causal pathway between low socioeconomic status and reduced transplant access, acting as a mediator in this relationship. If this relationship exists, interventions which successfully ameliorate the effects of low health literacy in clinical practice may have potential to improve outcomes, but also to reduce socioeconomic inequity. Possible interventions include health literacy-sensitive decision-making resources,[19] specific communication techniques,[20] enhanced educational programmes with direct support,[21, 22] patient advocacy,[23] or supported navigation of care pathways.[24] Further investigation with mediation analysis may be appropriate, and has been used to investigate the role of health literacy in other patient pathways. [25]

The ATTOM study benefits from a large representative sample of the UK incident dialysis population,[26] 2-years follow-up, high data completeness, robustness to missing data and detailed comorbidity adjustment. Limitations include use of the SILS to measure health literacy. Health literacy is a multifaceted concept,[6] so no measure can fully describe its different aspects, but longer comprehension tests such as STOFHLA (which tests comprehension of health related terms in sample medical information) do directly test different health literacy skills such as reading comprehension and numeracy. The SILS instead measures patient-reported perceived need for help when reading health-related material. The use of the SILS with limited health literacy defined as responses 'Sometimes', 'Often' or 'Always' as in this study has moderate accuracy in detecting limited health literacy defined by STOFHLA in patients with diabetes (sensitivity 54%; specificity 83%),[27] and on haemodialysis (Sensitivity 39%, Specificity 93%).[28] However, no health literacy measure can be relied on to provide a 'true' measure of health literacy because of the complexity of health literacy as a concept. Using a comprehension-based measure in studies with a large number

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of participants risks increasing research burden, reduced response rates (arguably more likely to be reduced among those with health literacy), and non-response bias. These factors influenced our choice of health literacy measure. Further, the simplicity of the SILS perhaps makes it more relevant to use in clinical practice, where patients who report difficulty understanding written information could quickly and easily be identified as at risk of reduced access to transplantation. Longer follow-up would have increased statistical power with more events accrued. Recruitment was not universal, but we estimate that over 50% of incident dialysis patients were recruited (based on comparison with registry data from 2012), and comparison of patients recruited vs not recruited showed no significant differences in demographics. We could not prospectively capture the processes of pre-emptive transplantation or pre-emptive listing because patients were recruited when starting dialysis. The baseline variable for pre-emptive deceased-donor transplant wait-listing does not capture patients who were listed then transplanted before starting dialysis. Baseline comorbidity data, while comprehensive, do not record severity of comorbidities or changes in comorbidity over time, so residual confounding is possible. No data were available on whether transplant work-up was performed or the results of this process, so any reasons for delay in transplant listing or transplantation (whether clinical or related to other factors) were not known. The highest proportion of missing data in complete-case analysis (Supplementary material 6) resulted from missing exposure (SILS) data. For the transplantation variables, a low proportion (under 8%) had any missing data in fully-adjusted analyses, and there was no significant difference in these outcomes between incomplete and complete cases. In analyses of baseline data, multiple imputation did not significantly change measured associations between health literacy and patient factors.[10] Imputation is unlikely to change results if the proportion of missing data is low.[29] Individual clinicians and renal centres may vary in their practice of deeming a patient suitable for transplant listing.[30] Centre-level differences in clinical practice are accounted for in our analysis by using robust standard errors, similar to methodology used elsewhere.[18] However, these methods do not investigate the reasons for centre variation, which lies outside the scope of this study but is investigated by our research

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group in a current study. Lastly, these findings from observational data provide evidence of independent associations but do not prove causation.

In conclusion, access to transplantation appears to be impeded by limited health literacy in a significant proportion of UK incident dialysis patients. These effects are unlikely to be unique to kidney transplantation processes, and may be applicable to other healthcare settings and disease pathways.[31] The impact of limited health literacy on the actions and interactions of patients, relatives and clinicians require further investigation. Examination of current practice and available support mechanisms, routine assessment for limited health literacy and development and testing of interventions to reduce its unwanted consequences would be helpful steps to improving equity of access to transplantation.[32, 33]

Methods

This prospective, multicentre cohort study was part of the Access to Transplant and Transplant Outcome Measures (ATTOM) programme. Patients starting dialysis aged 18-75 years, recruited December 2011 through September 2013 from all 72 UK renal centres provided informed, written consent for data collection. ATTOM methodology,[26] and baseline associations between limited health literacy, demographics and socioeconomic status[10] are published elsewhere. See **Figure 1** for the process of patient selection.

Baseline data

Within 90 days of starting dialysis, patients completed a questionnaire including demographics, individual-level indicators of socioeconomic status, and the Single Item Literacy Screener (SILS), a validated health literacy measure.[27, 28] The SILS is 'How often do you need to have someone help you when you read instructions, pamphlets or other written material from your doctor or pharmacy', with responses 1-Never, 2-Rarely, 3-Sometimes, 4-Often and 5-Always. Responses 'Sometimes',

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‘Often’ and ‘Always’ were taken to represent limited health literacy, informed by validation against the Short Test of Functional Health Literacy in Adults (STOFHLA, a 7-minute comprehension assessment).[27, 28] Primary renal diagnosis comorbidities, dialysis modality, vascular access and date of first contact with nephrology services were collected by structured review of clinical notes. Comorbidity was quantified using a Charlson comorbidity index modified for CKD populations (Supplementary methods 1, Table S8). Patients with self-reported English fluency below ‘good’ were excluded from primary analyses, but included in a sensitivity analysis.

Prospective data

Date of deceased-donor transplant listing and transplantation were received from National Health Service Blood and Transplant (NHSBT), and mortality data from the UK Renal Registry (UKRR), censored two years after recruitment. ‘Time to event’ variables included time from starting dialysis to listing for deceased-donor transplant, to transplantation from a living donor, to transplantation from any donor type (living or deceased), and to death (Figure 2). As patients were recruited after starting dialysis, those listed ‘pre-emptively’ (before starting dialysis) were not included in the time-to-event variable for transplant listing, but considered in a separate binary variable. Patients transplanted ‘pre-emptively’ were not included.

Analysis

Univariate analysis examined associations between limited health literacy and: ‘late presentation’ to nephrology (within 90 days of starting dialysis); initial dialysis modality; haemodialysis vascular access; pre-emptive listing for deceased-donor transplant; time to listing for deceased-donor transplant; time to living-donor transplantation; time to transplantation from any donor type and all-cause mortality. After listing for transplant, deceased-donor kidney offers are governed by organ allocation algorithms,[12] so are not influenced by health literacy, confirmed by analysis of time from listing to deceased-donor transplantation (Supplementary results 1).

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Multivariable analyses were performed for all outcome measures, with sequential adjustment for potential confounders known to be associated with the outcomes and with health literacy.[9, 10, 17, 18, 34] These were defined *a priori* and included age and sex, ethnicity and first language, comorbidity and primary renal diagnosis, and indicators of socioeconomic status[35] (highest educational qualification and car ownership). Effect ratios with robust standard errors were calculated in order to account for clustering within renal centres.[36]

Sensitivity analyses were performed. First, the models were re-fitted including patients who reported English fluency below 'very fluent', adjusted for fluency level in multivariable models. Second, multivariable analyses were repeated with adjustment for 2011 area-level deprivation score (Townsend)[37] in place of individual markers of socioeconomic status. Third, results were compared with and without robust standard errors to account for clustering by renal centre.

Data were described as mean (95% confidence interval), median [interquartile range], or number (percentage). Univariate analyses used t-tests, χ^2 test, and Kaplan-Meier analysis, and multivariable analysis used logistic regression, linear regression or Cox regression as appropriate. Statistical significance was defined *a priori* as $p<0.05$. Proportional hazards assumptions were tested using Schoenfeld residuals. Analyses presented used complete-case analysis. For each analysis, the proportion of missing data was calculated and results after multiple imputation of missing data are shown in the supplementary material. Patient characteristics and outcomes were compared between patients with missing vs complete data. All analyses used Stata 14.1 (StataCorp, USA).

Supplementary information is available at Kidney International's website

Author Contributions

Dominic M Taylor performed the analyses, produced the figures and tables and wrote the manuscript under the supervision of Rommel Ravanan, Paul Roderick and Simon Fraser. All other authors are members of the Access to Transplant and Transplant Outcome Measures (ATTOM)

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research group, and along with Rommel Ravanan and Paul Roderick, designed and ran the ATTOM study as a whole, and gave editorial and methodological advice during manuscript preparation.

Supplementary material headings

Supplementary results 1: Analysis of time from deceased-donor transplant listing to deceased-donor transplantation.

Supplementary results 2: Tests of the proportional hazards assumption

Supplementary results 3: Analysis including patients with moderate English fluency (or lower)

Table S1: Analysis including patients with moderate, low or no English fluency. Patient characteristics and univariable analysis by limited vs adequate health literacy

Table S2: Repeated multivariable analysis including patients with moderate, low or no English fluency.

Supplementary results 4: Townsend deprivation score

Table S3: Repeated multivariable analysis using Townsend deprivation score as a covariate

Supplementary results 5: Clustering by renal centre

Table S4: Effect ratios for each model before and after adjustment for clustering by renal centre

Supplementary results 6: Data completeness

Table S5: Missing data for each outcome variable.

Table S6: Comparison of demographics between patients with complete vs incomplete records for three transplant outcome analyses

Table S7: Comparison of results of multivariable analysis using complete cases only vs estimates from multiple imputation

Supplementary methods 1: Modified Charlson comorbidity index

Table S8: Score weightings for modified Charlson index based on Hemmelgarn et al

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Tables

Table 1: Summary statistics and univariate analysis by limited vs adequate health literacy

Shown as frequency (%), mean (95% CI) or median [IQR]. Subgroup percentages may not total 100% because of rounding. Significant p values shown in bold. Detailed baseline characteristics and associations with limited health literacy have been published separately.[10] Modified Charlson comorbidity index is described in supplementary material 1. Primary Renal Diagnoses were categorised according to UK Renal Registry (UKRR) criteria.

	Health Literacy		
	Adequate	**Limited**	
Total: 2463	**1915 (84)**	**359 (16)**	**p**
Demographics			
Male	1243 (65)	231 (64)	0.84
Age	58 [47, 67]	58 [47, 66]	0.67
Ethnicity:			
White	1651 (86)	304 (85)	
Asian	113 (6)	22 (6)	
Black	126 (7)	27 (8)	0.42
Chinese	9 (0.5)	0 (0)	
Mixed-race	10 (1)	4 (1)	
First language:			
English	1800 (94)	338 (94)	0.94
Other (but with good English fluency)	114 (6)	21 (6)	
Clinical features			
Primary renal diagnosis			
Diabetes	398 (21)	166 (47)	
Glomerulonephritis	305 (16)	40 (11)	
Pyelonephritis	124 (7)	18 (5)	
Hypertension	127 (7)	18 (5)	**<0.001**
Polycystic Kidney Disease	173 (9)	18 (5)	
Renovascular Disease	62 (3)	10 (3)	
Other	430 (23)	37 (10)	
Uncertain	275 (15)	46 (13)	
Modified Charlson Comorbidity index:			
0	881 (46)	77 (21)	
1-2	668 (35)	182 (51)	
3-4	233 (12)	66 (18)	**<0.001**
>4	133 (7)	34 (9)	

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	Health Literacy		
	Adequate	**Limited**	
Socioeconomic status indicators			
Highest educational qualification:			
None	551 (29)	179 (50)	
High School level	836 (44)	119 (33)	**<0.001**
University level	331 (17)	22 (6)	
Other qualification	189 (10)	39 (11)	
Car owner	1440 (75)	198 (55)	**<0.001**
Outcome measures			
Late presentation (<90 days before dialysis initiation)	291 (17)	32 (10)	**0.003**
Peritoneal Dialysis as first dialysis modality	417 (22)	61 (17)	**0.043**
Dialysis catheter as first vascular access (vs fistula; if haemodialysis was first modality)	809 (55)	164 (56)	0.68
Pre-emptive deceased-donor transplant listing	241 (13)	35 (10)	0.09
At 2 years from dialysis initiation:			
Listed for deceased-donor transplant	750 (42)	96 (27)	
Transplanted (living-donor)	162 (9)	7 (2)	
Transplanted (any donor type)	337 (18)	31 (9)	
Mortality	271 (14)	67 (19)	

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Table 2: Analysis of outcome measures by limited vs adequate health literacy, with sequential adjustment for demographics, primary renal diagnosis, comorbidity (modified Charlson index) and socioeconomic status (highest educational qualification and car ownership)

Measures of effect shown for limited vs adequate health literacy depend on the regression model used (Logistic: Odds ratio, OR; Linear: β coefficient; Cox: Hazard ratio, HR). Categorical variables for Ethnicity, first language, primary renal diagnosis, Comorbidity (modified Charlson index) and highest educational qualification are specified as shown in Table 1; Significant p-values are shown in bold. Patients with missing data for any variable in model 6 are excluded from all models, such that models 1-6 include the same sample.

		Model					
		1	2	3	4	5	6
		Unadjusted	+ Age/Sex	+ Ethnicity, first language	+ Primary renal diagnosis, Comorbidity	+ Highest educational qualification	+ Car ownership
Late presentation (<90 days) n=2001	OR (95% CI) p	0.55 (0.33,0.94) **0.027**	0.55 (0.32,0.93) **0.026**	0.55 (0.33,0.94) **0.028**	0.70 (0.39,1.27) 0.2	0.71 (0.39,1.28) 0.3	0.68 (0.37,1.24) 0.2
Peritoneal dialysis as first dialysis modality (vs haemodialysis) n=2214	OR (95% CI) p	0.73 (0.52,1.03) 0.08	0.73 (0.51,1.03) 0.08	0.73 (0.52,1.03) 0.08	0.76 (0.53,1.08) 0.1	0.84 (0.59,1.19) 0.3	0.93 (0.65,1.35) 0.7
Dialysis catheter as first vascular access (vs fistula; if haemodialysis was first modality) n=1741	OR (95% CI) p	1.07 (0.86,1.33) 0.6	1.06 (0.85,1.32) 0.6	1.05 (0.84,1.32) 0.6	1.12 (0.87,1.43) 0.4	1.12 (0.87,1.43) 0.4	1.09 (0.84,1.41) 0.5
Pre-emptive deceased-donor transplant listing n=2092	OR (95% CI) p	0.73 [0.52,1.02] 0.07	0.72 [0.52,1.01] 0.06	0.73 [0.52,1.02] 0.06	0.86 [0.60,1.21] 0.4	0.98 [0.68,1.41] 0.9	1.03 [0.71,1.49] 0.9
Likelihood of listing for deceased-donor transplant after starting dialysis n=1833	HR (95% CI) p	0.54 (0.41,0.73) **<0.001**	0.53 (0.39,0.72) **<0.001**	0.53 (0.40,0.71) **<0.001**	0.61 (0.45,0.82) **0.001**	0.66 (0.49,0.88) **0.004**	0.68 (0.51,0.91) **0.010**
Likelihood of living-donor transplantation after starting dialysis n=2180	HR (95% CI) p	0.23 (0.11,0.51) **<0.001**	0.24 (0.12,0.49) **<0.001**	0.24 (0.12,0.48) **<0.001**	0.32 (0.16,0.63) **0.001**	0.38 (0.20,0.75) **0.005**	0.41 (0.21,0.80) **0.009**
Likelihood of transplantation from any donor type after starting dialysis n=2178	HR (95% CI) p	0.47 (0.32,0.67) **<0.001**	0.47 (0.33,0.67) **<0.001**	0.47 (0.33,0.66) **<0.001**	0.54 (0.38,0.77) **0.001**	0.62 (0.43,0.89) **0.009**	0.65 (0.45,0.92) **0.016**
Mortality n=2186	HR (95% CI) p	1.27 (0.88,1.85) 0.2	1.29 (0.90,1.85) 0.2	1.30 (0.91,1.86) 0.2	1.13 (0.79,1.63) 0.5	1.07 (0.75,1.54) 0.7	1.05 (0.73,1.49) 0.8

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Figure Legends

Figure 1: Recruitment process

* The proportion of UK incident dialysis patients recruited to ATTOM is difficult to quantify because of differing start and end dates for each renal centre, although comparison with 2012 UK Renal Registry data showed that over 50% of incident dialysis patients under 75 years were recruited to ATTOM. A comparison of the characteristics of incident dialysis patients recruited to ATTOM and those registered with the UK Renal Registry (UKRR) showed no significant differences in age, sex or ethnicity after adjustment for missing ethnicity data in the UKRR record (data not shown).

† These patients were recruited after transplantation and re-recruited as incident dialysis patients after transplant failure

‡ Multi-organ transplants are subject to different organ allocation policies (compared to single-organ)

§ This is to account for the practice in some centres of listing before immediate suspension while investigations are performed to ensure fitness for transplantation

ATTOM: Access to Transplant and Transplant Outcome Measures

Figure 2:Specification of time-to-event variables

* This adjustment accounts for the practice of preparing patients for living-donor transplantation without adding them to the deceased-donor transplant waiting list, and assumes that the recipient is fit for transplantation 6 months before living-donor transplantation.

Figure 3: Univariate analysis of 'time to event' outcomes, with unadjusted Hazard Ratios (HRs) for limited vs adequate health literacy (HL)

Time-to-event outcomes specified as in Figure 2

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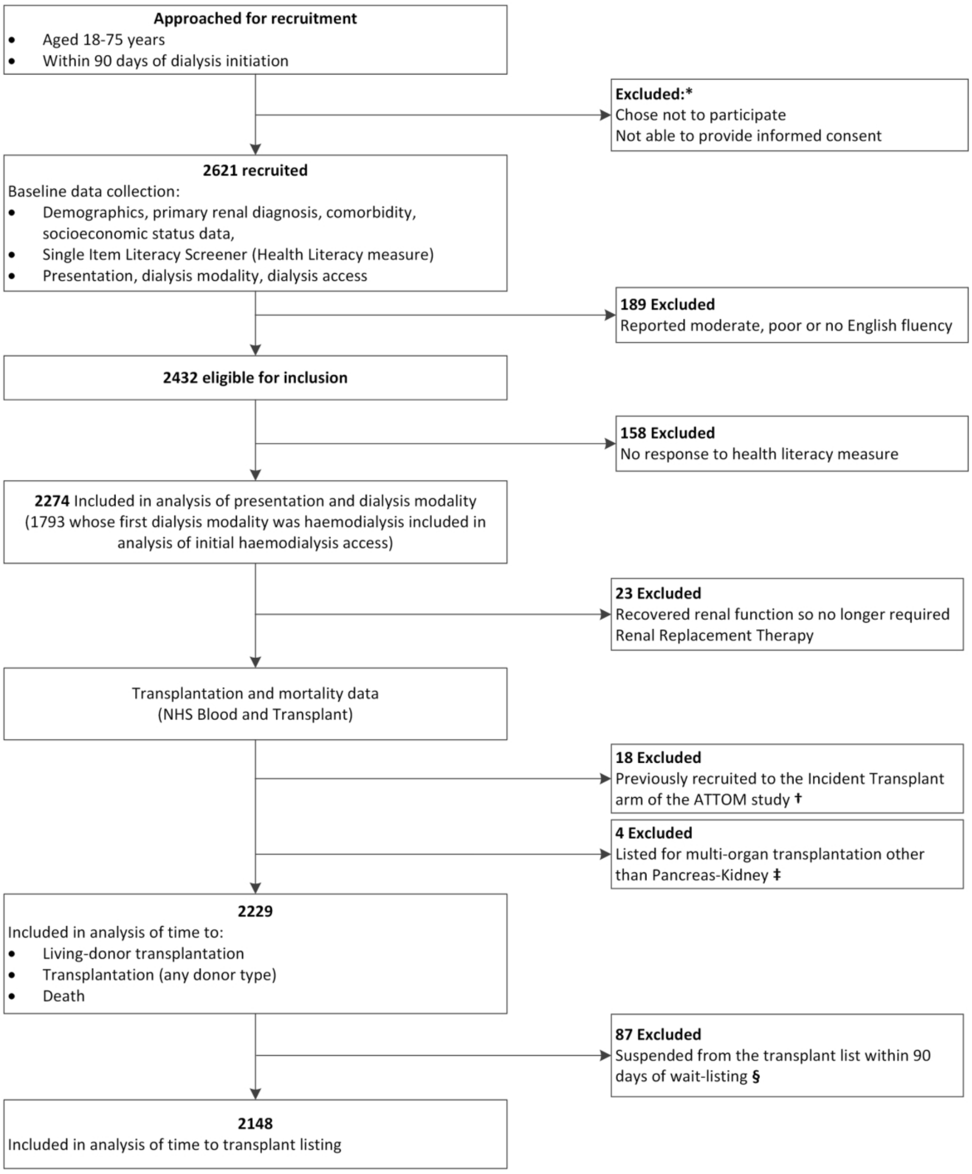

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ATTOM: Access to Transplant and Transplant Outcome Measures

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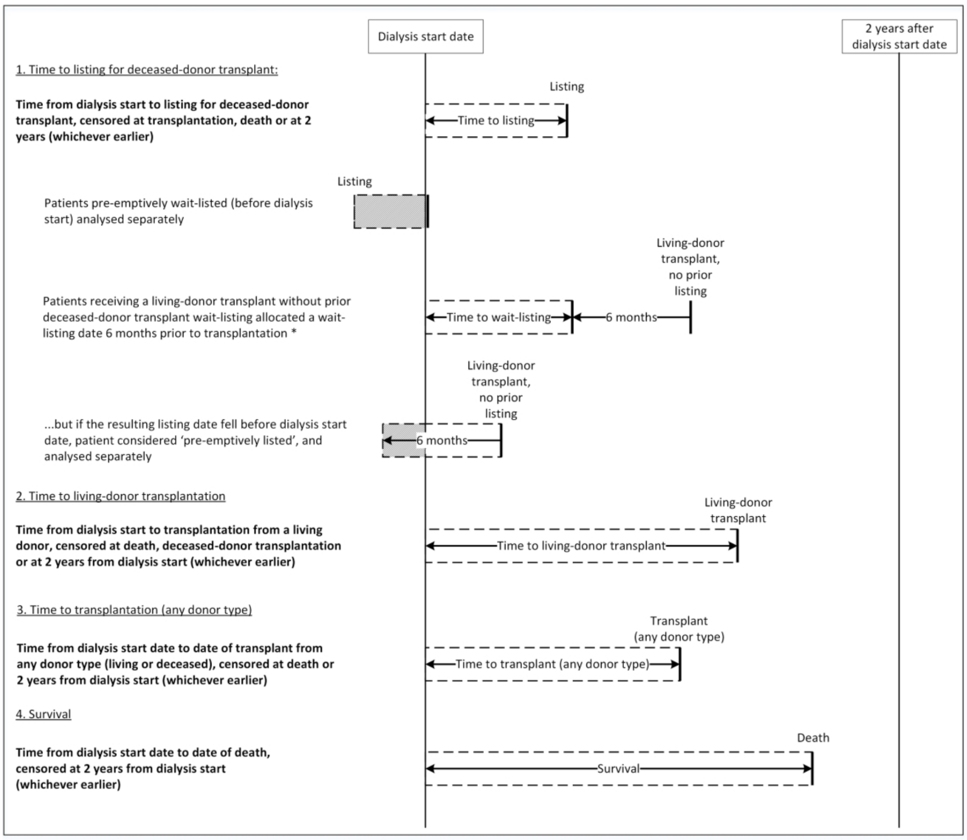

Figure 2: Specification of time-to-event variables
* This adjustment accounts for the practice of preparing patients for living-donor transplantation without adding them to the deceased-donor transplant waiting list, and assumes that the recipient is fit for transplantation 6 months before living-donor transplantation.

204x177mm (300 x 300 DPI)

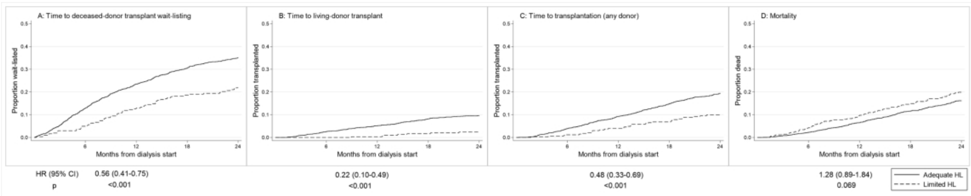

Figure 3: Univariate analysis of 'time to event' outcomes, with unadjusted Hazard Ratios (HRs) for limited vs adequate health literacy (HL)
Time-to-event outcomes specified as in Figure 2

203x40mm (300 x 300 DPI)

Supplementary results

1: Analysis of time from deceased-donor transplant listing to deceased-donor transplantation.

Patients were included if wait-listed prior to two years after dialysis start, and followed for two years from listing, until death or until removal from the transplant list, whichever was earlier. The proportional hazards assumption was not violated. The analysis included 802 patients. Hazard of deceased donor transplantation after listing for limited vs adequate health literacy was 0.92 (95% CI: 0.7, 1.25), p=0.6.

2: Tests of the proportional hazards assumption

Global tests of the proportional hazards (PH) assumption for the survival models shown in Table 2 were non-significant (no global violation of PH assumption). Individual-variable tests of the PH assumption were significant for some covariates in the model for time from dialysis start to transplant listing (one level of each of the categorical variables for ethnicity and primary renal diagnosis), the model for time to living-donor transplant (two levels of the categorical variable for ethnicity), and the model for time to any transplant (one level of the categorical variable for education and three levels of the categorical variable for primary renal diagnosis). Re-fitting each model with stratification of by these variables did not change the overall results.

3: Analysis including patients with moderate English fluency (or lower)

This analysis included 2463 patients, and included patients with moderate, poor or no English fluency. English fluency was then added as a categorical covariate in multivariable and mediation

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models (categories as in Table S1). Results of univariate analyses are shown in Table S1, and results of multivariable analyses are in Table S2.

There were no differences in the significance of results when compared to the primary analysis.

4: Townsend deprivation score

Townsend deprivation scores[S1] for each patient were derived from patient postcode and the UK census online Geoconvert service (http://geoconvert.mimas.ac.uk). These were used as covariates in multivariable models in place of individual-level markers of socioeconomic status. This did not change the overall significance of results compared to the primary analysis (Table S3).

5: Clustering by renal centre

Multivariable analyses were repeated with and without adjustment for clustering by renal centre (using robust standard errors). This adjustment did not significantly change results, shown in Table S4

6: Data completeness

Table S5 shows the proportion of missing data for multivariable analysis of each outcome variable. The largest proportion of missing data was for analysis of 'late presentation' (18%). The transplantation and mortality variables had a far lower proportion of missing data (6-8%). The majority of missing data for these analyses is from missing exposure data (no answer to SILS question). Comparison of patient characteristics between those with complete cases vs missing data for the three transplant variables is shown in Table S6. Patients with Asian ethnicity or with diabetes as primary renal diagnosis are over-represented in the missing data group.

Multiple imputation was performed to check for bias from the use of complete-case analysis, using 'imputation by chained equations' to generate 30 imputed datasets. As there were differences in the

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subjects included in different analyses (see figure 1), four sets of imputed datasets were generated: one for baseline analyses of late presentation, dialysis modality, pre-emptive transplant listing, one for analysis of dialysis access, one for analyses of time to living-donor transplantation, any transplant or death, and one for analysis of time to transplant wait-listing. Estimated effect-sizes after full-adjustment for each outcome using 30 imputed datasets are shown in Table S7. There were no major differences in the significance of the results from these analyses compared to complete-case analysis.

References

S1. Townsend P, Phillimore P, Beatie A. Health and Deprivation: inequality and the North. *Croom Helm Ltd*, 1988.

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Supplementary methods: Modified Charlson comorbidity index

This index was developed from Hemmelgarn et al (2003),[S2] who adapted the original Charlson index[S3] 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. Scoring for the Hemmelgarn modified Charlson index, and the scoring used for this study are shown in Table S8

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 analyses.

References

S2. Hemmelgarn B, Manns B, Quan H, et al. Adapting the Charlson Comorbidity index for use in patients with ESRD. Am J Kidney Dis 2003; 42: 125-132.

S3. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-383.

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Table S1:Analysis including patients with moderate, low or no English fluency. Patient characteristics and univariable analysis by limited vs adequate health literacy

Shown as frequency (%), mean (95% CI) or median [IQR]. Subgroup percentages may not total 100% because of rounding. Significant p values shown in bold. Modified Charlson comorbidity index is described in supplementary material 1. Primary renal diagnoses were categorised according to UK Renal Registry (UKRR) criteria.

	Health Literacy		
	Adequate	Limited	
Total: 2463	1982 (80)	481 (20)	p
Male	1294 (65)	311 (65)	0.80
Age	58 [47, 67]	58 [47, 66]	0.64
Ethnicity:			
White	1,665 (84)	319 (67)	
Asian	152 (8)	111 (23)	
Black	135 (7)	39 (8)	<0.001
Chinese	12 (1)	5 (1)	
Mixed-race	12 (1)	4 (1)	
Language:			
English First Language	1,800 (91)	338 (70)	
Other first language, self-reported English Fluency:			
Good	114 (6)	21 (4)	<0.001
Moderate	54 (3)	58 (12)	
Poor or no English	13 (1)	64 (13)	
Modified Charlson Comorbidity index			
0	913 (46)	124 (26)	
1-2	692 (35)	230 (48)	
3-4	240 (12)	89 (19)	<0.001
>4	137 (7)	38 (8)	
Primary Renal Diagnosis			
Diabetes	417 (21)	216 (46)	
Glomerulonephritis	314 (16)	59 (13)	
Pyelonephritis	128 (7)	20 (4)	
Hypertension	128 (7)	24 (5)	<0.001
Polycystic Kidney Disease	178 (9)	21 (4)	
Renovascular Disease	65 (3)	11 (2)	
Other	444 (23)	53 (11)	
Uncertain	286 (15)	68 (14)	

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	Health Literacy		
	Adequate	Limited	
Highest educational qualification:			
None	568 (29)	245 (51)	
High School level	858 (43)	156 (33)	**<0.001**
University level	355 (18)	39 (8)	
Other qualification	193 (10)	40 (8)	
No educational qualifications (vs any)	568 (29)	245 (51)	**<0.001**
Car owner	1479 (75)	272 (57)	**<0.001**
Late presentation (<90 days before dialysis initiation)	299 (17)	41 (10)	**0.001**
Peritoneal Dialysis as initial dialysis modality	424 (21)	81 (17)	**0.028**
Dialysis catheter as first vascular access (vs fistula; if haemodialysis was first modality)	839 (55)	223 (57)	0.39
Pre-emptive deceased-donor transplant listing	247 (13)	44 (10)	**0.030**
At 2 years from dialysis initiation:			
Listed for deceased-donor transplant	777 (42)	145 (31)	
Transplanted (living-donor)	167 (9)	15 (3)	
Transplanted (any donor type)	346 (18)	45 (10)	
Mortality	277 (14)	82 (17)	

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Table S1:Repeated multivariable analysis including patients with moderate, low or no English fluency.

Measures of effect shown for limited vs adequate health literacy depend on the regression model used (Logistic: Odds ratio, OR; Cox: Hazard ratio, HR). Categorical variables for ethnicity, English fluency, first language, primary renal diagnosis, comorbidity (modified Charlson index) and highest educational qualification are specified as in Table 1; Significant p-values are shown in bold.

		Model					
		1 Unadjusted	2 + Age/Sex	3 + Ethnicity, first language	4 + Primary renal diagnosis, Comorbidity	5 + Highest educational qualification	6 + Car ownership
Late presentation (<90 days) n=2147	OR (95% CI) p	0.55 (0.36,0.83) **0.005**	0.54 (0.36,0.83) **0.005**	0.56 (0.34,0.92) **0.023**	0.69 (0.39,1.21) 0.2	0.71 (0.40,1.25) 0.2	0.67 (0.38,1.19) 0.2
Peritoneal dialysis as first dialysis modality (vs haemodialysis) n=2395	OR (95% CI) p	0.73 (0.56,0.96) **0.025**	0.73 (0.55,0.96) **0.024**	0.75 (0.55,1.03) **0.07**	0.78 (0.57,1.08) 0.1	0.87 (0.63,1.19) 0.4	0.96 (0.69,1.34) 0.8
Dialysis catheter as first vascular access (vs fistula; if haemodialysis was first modality) n=1892	OR (95% CI) p	1.11 (0.92,1.33) 0.3	1.10 (0.92,1.33) 0.3	1.04 (0.84,1.30) 0.7	1.09 (0.84,1.40) 0.5	1.09 (0.85,1.39) 0.5	1.05 (0.82,1.35) 0.7
Pre-emptive deceased-donor transplant listing n=2275	OR (95% CI) p	0.68 (0.51,0.92) **0.013**	0.68 (0.50,0.92) **0.013**	0.73 (0.53,0.99) **0.046**	0.86 (0.63,1.16) 0.3	0.97 (0.71,1.34) 0.9	1.03 (0.75,1.41) 0.9
Likelihood of listing for deceased-donor transplant after starting dialysis n=1994	HR (95% CI) p	0.68 (0.54,0.85) **0.001**	0.67 (0.52,0.87) **0.002**	0.59 (0.47,0.74) **<0.001**	0.64 (0.50,0.82) **<0.001**	0.68 (0.53,0.88) **0.003**	0.70 (0.54,0.91) **0.008**
Likelihood of living-donor transplantation after starting dialysis n=2361	HR (95% CI) p	0.35 (0.21,0.57) **<0.001**	0.36 (0.23,0.56) **<0.001**	0.32 (0.21,0.51) **<0.001**	0.39 (0.24,0.63) **<0.001**	0.46 (0.28,0.75) **0.002**	0.48 (0.30,0.78) **0.003**
Likelihood of transplantation from any donor type after starting dialysis n=2358	HR (95% CI) p	0.50 (0.38,0.66) **<0.001**	0.51 (0.40,0.66) **<0.001**	0.51 (0.39,0.67) **<0.001**	0.58 (0.44,0.77) **<0.001**	0.65 (0.47,0.89) **0.007**	0.68 (0.50,0.93) **0.016**
Mortality n=2367	HR (95% CI) p	1.17 (0.82,1.68) 0.4	1.19 (0.84,1.69) 0.3	1.32 (0.93,1.87) 0.1	1.15 (0.81,1.63) 0.4	1.08 (0.76,1.53) 0.6	1.06 (0.75,1.49) 0.8

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Table S3:Repeated multivariable analysis using Townsend deprivation score as a covariate

Measures of effect shown for limited vs adequate health literacy depend on the regression model used (Logistic: Odds ratio, OR; Cox: Hazard ratio, HR). Categorical variables for ethnicity, English fluency, first language, primary renal diagnosis, comorbidity (modified Charlson index) and highest educational qualification are specified as in **Error! Reference source not found.**; Significant p-values are shown in bold.

		Model				
		1 Unadjusted	2 + Age/Sex	3 + Ethnicity, first language	4 + Primary renal diagnosis, Comorbidity	5 + Townsend deprivation score
Late presentation (<90 days)	OR (95% CI)	0.56 (0.33,0.95)	0.56 (0.33,0.95)	0.56 (0.33,0.95)	0.71 (0.39,1.29)	0.68 (0.37,1.25)
n=1993	p	**0.032**	**0.030**	**0.033**	0.3	0.2
Peritoneal dialysis as first dialysis modality (vs haemodialysis)	OR (95% CI)	0.75 (0.53,1.06)	0.75 (0.53,1.06)	0.75 (0.53,1.06)	0.78 (0.55,1.10)	0.84 (0.59,1.21)
n=2209	p	0.1	0.1	0.1	0.2	0.4
Dialysis catheter as first vascular access (vs fistula; if haemodialysis was first modality)	OR (95% CI)	1.07 (0.86,1.34)	1.07 (0.85,1.33)	1.06 (0.85,1.33)	1.13 (0.88,1.44)	1.09 (0.84,1.42)
n=1739	p	0.6	0.6	0.6	0.4	0.5
Pre-emptive deceased-donor transplant listing	OR (95% CI)	0.73 (0.52,1.02)	0.72 (0.51,1.01)	0.72 (0.52,1.01)	0.85 (0.60,1.20)	0.94 (0.66,1.36)
n=2087	p	0.06	0.06	0.06	0.3	0.8
Likelihood of listing for deceased-donor transplant after starting dialysis	HR (95% CI)	0.56 (0.42,0.75)	0.55 (0.41,0.73)	0.54 (0.41,0.72)	0.62 (0.47,0.84)	0.66 (0.48,0.89)
n=1828	p	**<0.001**	**<0.001**	**<0.001**	**0.002**	**0.007**
Likelihood of living-donor transplantation after starting dialysis	HR (95% CI)	0.24 (0.11,0.52)	0.24 (0.12,0.50)	0.24 (0.12,0.48)	0.32 (0.16,0.63)	0.35 (0.18,0.70)
n=2175	p	**<0.001**	**<0.001**	**<0.001**	**0.001**	**0.003**
Likelihood of transplantation from any donor type after starting dialysis	HR (95% CI)	0.48 (0.34,0.69)	0.49 (0.35,0.69)	0.48 (0.34,0.68)	0.56 (0.39,0.79)	0.60 (0.42,0.86)
n=2173	p	**<0.001**	**<0.001**	**<0.001**	**0.001**	**0.006**
Mortality	HR (95% CI)	1.26 (0.87,1.83)	1.28 (0.89,1.83)	1.29 (0.90,1.85)	1.12 (0.78,1.61)	1.11 (0.77,1.58)
n=2181	p	0.2	0.2	0.2	0.5	0.6

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Table S4: Effect ratios for each model before and after adjustment for clustering by renal centre

Measures of effect shown for limited vs adequate health literacy depend on the regression model used (Logistic: Odds ratio, OR; Cox: Hazard ratio, HR). Categorical variables for ethnicity, English fluency, first language, primary renal diagnosis, comorbidity (modified Charlson index) and highest educational qualification are specified as in **Error! Reference source not found.**; Significant p-values are shown in bold. Adjustment for clustering by renal centre used robust standard errors.

		Effect ratios, after adjustment for age, sex, ethnicity, first language, primary renal diagnosis, comorbidity, education and car ownership	
		Before adjustment for clustering	After adjustment for clustering
Late presentation (<90 days) n=2001	OR (95% CI) p	0.68 (0.44, 1.03) 0.07	0.68 (0.37, 1.24) 0.2
Peritoneal dialysis as first dialysis modality (vs haemodialysis) n=2214	OR (95% CI) p	0.93 (0.67, 1.29) 0.7	0.93 (0.65, 1.35) 0.7
Dialysis catheter as first vascular access (vs fistula; if haemodialysis was first modality) n=1741	OR (95% CI) p	1.09 (0.83, 1.43) 0.6	1.09 (0.84, 1.41) 0.5
Pre-emptive deceased-donor transplant listing n=2092	OR (95% CI) p	1.03 (0.68, 1.57) 0.9	1.03 (0.71, 1.49) 0.9
Likelihood of listing for deceased-donor transplant after starting dialysis n=1833	HR (95% CI) p	0.68 (0.51, 0.90) **0.007**	0.68 (0.51, 0.91) **0.010**
Likelihood of living-donor transplantation after starting dialysis n=2180	HR (95% CI) p	0.41 0.19, 0.88) **0.023**	0.41 0.21, 0.80) **0.009**
Likelihood of transplantation from any donor type after starting dialysis n=2178	HR (95% CI) p	0.65 (0.44, 0.96) **0.032**	0.65 (0.45, 0.92) **0.016**
Mortality n=2186	HR (95% CI) p	1.05 (0.79, 1.39) 0.8	1.05 (0.73, 1.49) 0.8

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Table S5: Missing data for each outcome variable.

The first column shows the total number or patients eligible for inclusion in each analysis after the exclusions shown in Figure 1. For each analysis, number of patients with missing data for the outcome, exposure (SILS) and covariates are shown, and the proportion of eligible patients included in complete case analysis are shown in the right-hand column. In the fully-adjusted model for initial dialysis modality, 13 further observations were excluded because in one category of ethnic group, no patients were treated with peritoneal dialysis.

	Total eligible for inclusion (excluding moderate/low English fluency)	Missing data for outcome variable	Missing SILS data (if outcome data not missing)	Missing covariate data (If SILS/outcome data not missing and multivariable analysis performed)	Complete cases (% of total eligible)
Late presentation	**2432**	**274**	**131**	**26**	**2001 (82)**
Initial dialysis modality	**2432**	**4**	**157**	**44**	**2227 (92) ***
Dialysis access (if initial dialysis modality was haemodialysis)	**1909**	**26**	**110**	**32**	**1741 (91)**
Transplant listing	**2000**	**5**	**126**	**36**	**1833 (92)**
Living-donor transplantation	**2382**	**5**	**152**	**45**	**2180 (92)**
Transplantation (any donor)	**2380**	**5**	**152**	**45**	**2178 (92)**
Survival	**2387**	**1**	**154**	**46**	**2186 (92)**

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Table S6: Comparison of demographics between patients with complete vs incomplete records for three transplant outcome analyses

	Transplant listing			Living-donor transplantation			Transplantation (any donor)		
	Complete cases n=1835	Missing data n=160	p	Complete cases n=2182	Missing data n=200	p	Complete cases n=2180	Missing data n=200	p
Median age [IQR]	59 [48-68]	60 [49-67]	0.90	58 [47-67]	58 [45-66]	0.34	58 [47-67]	58 [45-66]	0.33
Male	1204 (66)	99 (62)	0.34	1413 (65)	123 (62)	0.36	1411 (65)	123 (62)	0.36
Ethnicity:									
White	1585 (86)	109 (71)		1884 (86)	142 (74)		1882 (86)	142 (74)	
Asian	103 (6)	30 (20)		131 (6)	32 (17)		131 (6)	32 (17)	
Black	128 (7)	9 (6)	<0.001	146 (7)	13 (7)	<0.001	146 (7)	13 (7)	<0.001
Chinese	8 (0.4)	2 (1)		8 (0.4)	2 (1)		8 (0.4)	2 (1)	
Mixed-race	11 (1)	2 (1)		13 (1)	2 (1)		13 (1)	2 (1)	
English first language	1726 (94)	33 (94)	0.96	2050 (94)	44 (96)	0.63	2048 (94)	44 (96)	0.63
Modified Charlson index									
0	707 (39)	64 (40)		914 (42)	86 (43)		915 (42)	86 (43)	
1-2	694 (38)	70 (44)	0.16	813 (37)	85 (43)	0.16	810 (37)	85 (43	0.15
3-4	279 (15)	18 (11)		294 (13)	20 (10)		294 (13)	20 (10)	
>_5	155 (8)	8 (5)		161 (7)	9 (5)		161 (7)	9 (5)	
Primary renal diagnosis: Diabetes	478 (26)	54 (39)	0.002	312 (14)	12 (7)	0.001	549 (25)	65 (38)	0.001
No educational qualifications (vs any)	1194 (65)	20 (71)	0.48	1475 (68)	29 (74)	0.37	1472 (68)	29 (74)	0.37

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Table S7: Comparison of results of multivariable analysis using complete cases only vs estimates from multiple imputation

All results after adjustment for age, sex, ethnicity, first language, primary renal diagnosis, comorbidity, education and car ownership, with robust standard errors to account for clustering by renal centre. Results from imputed data are estimated from 30 imputed datasets.

		Unimputed	Imputed
Late presentation	OR	0.68	0.66
(<90 days)	(95% CI)	(0.37,1.24)	(0.39,1.14)
n=2001 (complete-case analysis); n= 2432 (multiple imputation estimate)	p	0.2	0.136
Peritoneal dialysis as first dialysis modality	OR	0.93	0.93
(vs haemodialysis)	(95% CI)	(0.65,1.35)	(0.66,1.32)
n=2214 (complete-case analysis); n=2432 (multiple imputation estimate)	p	0.7	0.7
Dialysis catheter as first vascular access	OR	1.09	1.08
(vs fistula; if haemodialysis was first modality)	(95% CI)	(0.84,1.41)	(0.83,1.41)
n=1741 (complete-case analysis); n=1909 (multiple imputation estimate)	p	0.5	0.5
Pre-emptive deceased-donor transplant listing	OR	1.03	1.04
	(95% CI)	[0.71,1.49]	(0.71,1.49)
n=2092 (complete-case analysis); n=2432 (multiple imputation estimate)	p	0.9	0.9
Likelihood of listing for deceased-donor transplant after starting dialysis	HR	0.68	0.70
	(95% CI)	(0.51,0.91)	(0.52,0.94)
n=1833 (complete-case analysis); n= ___ (multiple imputation estimate)	p	**0.010**	**0.016**
Likelihood of living-donor transplantation after starting dialysis	HR	0.41	0.40
	(95% CI)	(0.21,0.80)	(0.20,0.80)
n=2180 (complete-case analysis); n=2377 (multiple imputation estimate)	p	**0.009**	**0.009**
Likelihood of transplantation from any donor type after starting dialysis	HR	0.65	0.64
	(95% CI)	(0.45,0.92)	(0.44,0.93)
n=2178 (complete-case analysis); n=2373 (multiple imputation estimate)	p	**0.016**	**0.019**
Mortality	HR	1.05	1.05
	(95% CI)	(0.73,1.49)	(0.75,1.47)
n=2186 (complete-case analysis); n=2378 (multiple imputation estimate)	p	0.8	0.8

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Table S8: 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
	33		31

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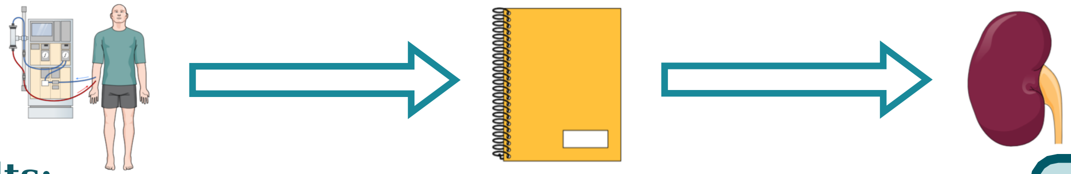
Limited health literacy is associated with reduced access to kidney transplantation



Over 2000 UK adults:

- starting dialysis
- with good English fluency
- aged 18-75 years...

Limited health literacy

was independently associated with reduced chance

(adjusted for demographics, primary renal diagnosis, comorbidity and socioeconomic status)

Transplant listing
(HR: 0.68; 95% CI: 0.51-0.91)

Living-donor transplantation
(HR: 0.41; 95% CI: 0.21-0.80)

Transplantation from any donor type
(HR: 0.65; 0.45-0.92)

CONCLUSION:

Limited health literacy is associated with reduced access to transplantation.

Health literacy-related interventions may improve transplant access

Dominic Taylor et al 2018

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The International Society of Nephrology (http://www.isn-online.org/site/cms)

Results

after controlling for demographics, clinical