Patient-relevant outcomes after kidney transplantation
Wang, Y.

Chapter 2

Illness perceptions and medication adherence in patients after successful kidney transplantation: a cross-sectional study

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Abstract

Background: Medication non-adherence to immunosuppressants is a well-known risk factor for suboptimal health outcomes in kidney transplant recipients (KTRs). This study examined the relationship between illness perceptions and medication non-adherence in prevalent Dutch KTRs and whether this relationship depended on post-transplant time.

Methods: Eligible KTRs transplanted in Leiden University Medical Center were invited for this cross-sectional study. The illness perceptions and medication non-adherence were measured via validated questionnaires. Associations between illness perceptions and medication non-adherence were investigated using multivariable logistic regression models.

Results: 627 participating KTRs were analyzed. 203 (32.4%) KTRs were considered nonadherent to their immunosuppressants with 'taking medication more than 2 hours from the prescribed dosing time' as the most prevalent nonadherent behavior (n=171; 27.3%). Three illness perceptions were significantly associated with medication non-adherence: *illness identity* (adjusted odds ratio [OR_{adj}]=1.07; 95% confidence interval [CI], 1.00-1.14), *concern* (OR_{adj}=1.07; 95% CI,1.00-1.14), and *illness coherence* (OR_{adj}=1.11; 95% CI,1.01-1.22). The relationships between illness perceptions and medication non-adherence did not differ depending on post-transplant time *(*p-values ranged from 0.48 to 0.96).

Conclusion: Stronger negative illness perceptions are associated with medication non-adherence to immunosuppressants. Targeting negative illness perceptions by means of psychoeducational interventions could optimize medication adherence and consequently improve health outcomes in KTRs.

Introduction

Successful kidney transplantation requires strict adherence to chronic immunosuppressive regimens[1]. Failure to take immunosuppressants as prescribed has been identified as a risk factor for adverse clinical outcomes among kidney transplant recipients (KTRs), including graft loss and reduced patient survival[2, 3]. Butler et al. reported a seven-fold higher odds of graft failure in nonadherent KTRs than in adherent KTRs[2]. Furthermore, persistent medication non-adherence can lead to increased individual medical costs[4]. Despite the obvious negative impact, medication non-adherence in KTRs remains substantial, with a broadly consistent prevalence of 20% or higher[1, 5].

Leventhal's widely-used Common Sense Model (CSM) of Self-regulation provides us with explanations for patients' behavior when facing health threats and may aid our understanding of the behavioral mechanism explaining medication non-adherence[6]. According to the CSM, patients' illness perceptions directly influence their coping behavior(e.g. medication adherence) with the medical condition; thereafter, they appraise the effect of such behavioral adaptions and the result of the appraisal thereof can shape their illness perceptions[6]. Consequently, illness perceptions – referring to patients' appraisal and understanding of their medical condition – are considered a potential intervention target to improve coping behaviors and subsequent health outcomes.

Previous studies have shown that illness perceptions are associated with various outcomes in patients with chronic conditions, including chronic kidney disease[7-10]. In non-KTRs (e.g. patients with hypertension), stronger positive illness perceptions have also been found associated with better medication adherence[11]. However, very few studies have shed light on illness perceptions and their associations with medication non-adherence in patients after kidney transplantation, and the existing studies found inconsistent results: Cossart et al.[12] found stronger positive perceptions (i.e. illness coherence) in adherent KTRs, while Massey et al.[13] described a downward trend in medication adherence with improved illness perceptions over time. Therefore, further studies are necessary to understand the influence of illness perceptions on medication non-adherence and to develop effective patient-centered interventions to improve medication adherence in this KTR population.

Finally, the dynamic nature of the self-regulation process is an important feature of the CSM, which suggests that illness perceptions can change throughout the course of a disease.[14, 15] A previous study has detected changes in certain illness perceptions in KTRs within 1.5 years after transplantation.[13] It is reasonable to speculate that the relief after successful kidney transplantation may positively impact illness perceptions in the short term; however,

in the long term, illness perceptions may change due to changes in the experience of immunosuppressant-related side effects. Until now, little is known about whether such dynamic feature of KTRs' illness perceptions also plays a role in medication adherence. Therefore, in this study, we will investigate the influence of illness perceptions on medication non-adherence to immunosuppressants among prevalent Dutch KTRs and explore whether such associations differ depending on the time since their kidney transplant.

Patients and Methods

For the reporting of this study, we followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline[16].

Study design and study population

This study was conducted in Leiden University Medical Center (LUMC) from October 1, 2020 to October 30, 2020. KTRs who met the following criteria were invited to participate in this study: 1) adult KTRs transplanted before April 1, 2019 in LUMC with a functioning graft; 2) the last visit in LUMC took place after December 31, 2010; 3) patients with a sufficient understanding of the Dutch language. To avoid overburdening of patients, we did not invite patients transplanted after April 2019 as they were already involved in a longitudinal study to measure patient-reported outcomes after kidney transplantation routinely. We excluded patients whose last visit in LUMC was before December 31, 2010 to have a more actively-followed patient population. The questionnaires used in our study were sent to patients via postal service or email along with an informed consent form to use the collected data for research purposes. The questionnaires measured medication adherence and illness perceptions, and collected data about patients' education level, marital status and employment status at the time of the study. A reminder email was sent to patients with a known email address if they did not respond within 7 days after the first invitation. The institutional review board of LUMC for non-WMO research (i.e. research not subjected to the Medical Research Involving Human Subjects Act [WMO]) approved this study. The study was conducted following the national guidelines for medical scientific research[17].

Medication non-adherence

Self-reported medication adherence to immunosuppressants was measured using a commonly used and validated questionnaire, the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS© Written)[18]. The questionnaire contains four questions to measure medication adherence in the implementation phase (i.e. issue with taking, changed timing, drug holidays and dose reduction). Each question asks the occurrence

of the medication-taking behavior (yes or no) and the frequency of corresponding nonadherent behavior (i.e. once a month, once every two weeks, every week, more than once a week, and every day) in the past four weeks prior to the measurement. Regardless of the frequency, any "yes" to the above four questions implied medication non-adherence to immunosuppressants. The reporting of medication adherence followed the ESPACOMP Medication Adherence Reporting Guidelines (EMERGE) checklist[19].

Illness perceptions

The following eight illness perceptions were measured on a 0-to-10 response scale using the commonly used and validated questionnaire, the Brief Illness Perception Questionnaire (Brief-IPQ)[20]: *consequences*, *timeline*, *personal control*, *treatment control*, *illness identity*, *concern*, *illness coherence* and *emotional response*. In this study, we omitted illness perception domain *cause* from our analysis as the cause of kidney disease is very heterogeneous[7]. To facilitate interpretation, we recoded the scores of three perceptions (i.e. *personal control*, *treatment control* and *illness coherence*) in such a way that for all perceptions, a higher score indicated more negative illness perceptions (e.g. a higher score of treatment control now implies a lower belief of patients in that the treatment they receive can relieve or cure their illness).

Sociodemographic and clinical characteristics

Data on sociodemographic and clinical characteristics were collected via questionnaires or from patients' medical records, including age at transplantation, age at study participation, sex, socioeconomic status (SES), education level, marital status, number of transplantation, primary kidney disease, donor type (living donor and deceased donor), pre-emptive kidney transplantation, time since kidney transplantation (i.e. post-transplant time), body mass index (BMI), comorbidities and type of immunosuppressants at study. The SES of study participants was obtained by linking the four digits of their postcode with the latest SES-score per postcode area reported by the Netherlands Institute for Social Research; the SES was divided into three groups: low, medium and high[21]. Primary kidney disease (PKD) was classified into eight categories: congenital and hereditary kidney disease, cystic kidney disease, diabetes mellitus, glomerulonephritis, renal vascular disease, interstitial nephritis/pyelonephritis, other diseases, and unknown ontology[22]. Data about comorbidities at transplantation were collected. Comorbidities were indicated by a history of diabetes mellitus, cardiac event, vascular event and cerebrovascular event before the study. Post-transplant time was categorized into three groups: ≤5 years, 5-15 years, and >15 years. The most recent BMI was also collected, with the average time between BMI measurement and study participation being approximately one year (mean=12.5 months; SD=13.7 months).

Statistical analysis

Continuous variables were presented as mean with standard deviation (SD) if normally distributed and as median with interquartile range (IQR) if not normally distributed. Count (percentage) was used for categorical variables. Medication adherence and illness perceptions were described in the total study population and in subgroups stratified by post-transplant time. Multivariable logistic regression models were employed to analyze the impact of each separate illness perception on medication adherence while adjusting for potential confounders, including age at study participation, sex, SES, marital status, education level, employment status, donor type, number of transplantation, PKD, comorbidities and post-transplant time. The interaction term 'post-transplant time (categorical) * illness perception' was added to evaluate whether the influence of individual illness perception on medication non-adherence differed depending on post-transplant time. A variable "IPQ score / n" was used in the logistic regression models to assess the risk of medication non-adherence with n increments in IPQ-score (i.e. one or two increments on an 11-point scale).

Missing values were considered 'missing at random' and were imputed with 10-folds multiple imputation[23]. In addition to the variables with missing values (see **Table 1**), variables used for multiple imputation included illness perceptions, medication adherence and other variables adjusted for in the logistical regression model. Abnormally distributed continuous variables were log-transformed for imputation. As sensitivity analyses, we repeated all analyses but now excluded comorbidities and BMI from the multivariable model due to a relatively high percentage of missing values. The patient characteristics of responders and non-responders are presented in **Table S1**. *P*-value <0.05 was considered significant. We used SPSS software version 25.0. (IBM, Armonk, NY, USA) for all analyses.

Results

Of the 1700 adult KTRs who were transplanted before April 1, 2019, at LUMC and met study inclusion criteria, 743 (43.7%) KTRs responded via email (n=606) or via postal service (n=137). 39 responders filled out the questionnaires but did not want to participate in this study. After excluding another 77 patients who received simultaneous pancreas-kidney transplantation, 627 KTRs were left to be included in the main analysis (**Figure 1**). Please see **Table S1** for the characteristics of the non-responders.

Patient characteristics

Table 1 shows the sociodemographic and clinical characteristics of the responders in the total population and stratified by post-transplant time. The mean (SD) age of all included KTRs at study participation was 61.4 (11.3) years old; 93% of the KTRS were between 40 to 80 years old at the study; the median (IQR) post-transplant time was 9.0 (10.2) years; 74.5% of the KTRs had a partner; 89.8% had a medium or high SES; 57.4% received a high level of education; and 89.0% were employed, retired or students. After stratification, KTRs with a post-transplant time of more than 15 years had the oldest age at study participation, the youngest age when receiving the transplantation, and the highest percentage of deceased donor kidney transplantation. KTRs with a post-transplant time of less than 5 years had the highest unemployment rate and the lowest percentage of living alone or being separated. Notably, the percentages of patients with diabetes as either PKD or comorbidity reduced as the post-transplant time increased. Difference in immunosuppressants was also observed in KTRs with different post-transplant time: patients with a post-transplant time of more than 15 years were less likely to receive prednisone, tacrolimus, and mycophenolic acid in comparison to the other two groups. Compared to the non-responders, the study population had higher SES ranks and a lower percentage of diabetes as their PKD (**Table S1**).

Medication non-adherence

Table 2 presents self-reported non-adherence to immunosuppressants in all study participants: 203 (32.4%) KTRs were identified as nonadherent based on the BAASIS-scoring algorithm. When focusing on the specific medication non-adherence domains, the results showed that non-adherence to *timing* (i.e. taking medication with more than 2 hours difference from the prescribed time; 27.3%) was the most frequently reported nonadherent behavior, followed by *issue with taking* (i.e. not take medication sporadically; 12.3%). Very few KTRs reported *drug holiday* (i.e. not take medication consecutively; 0.8%) or *dose reduction* (i.e. reduce the dosage of prescribed medication; 0.4%). Most nonadherent KTRs reported nonadherent behavior once a month. After stratification by post-transplant time, the results showed that the proportion of nonadherent patients increased as the time after kidney transplantation increased in the overall and in the separate nonadherent behavior domains.
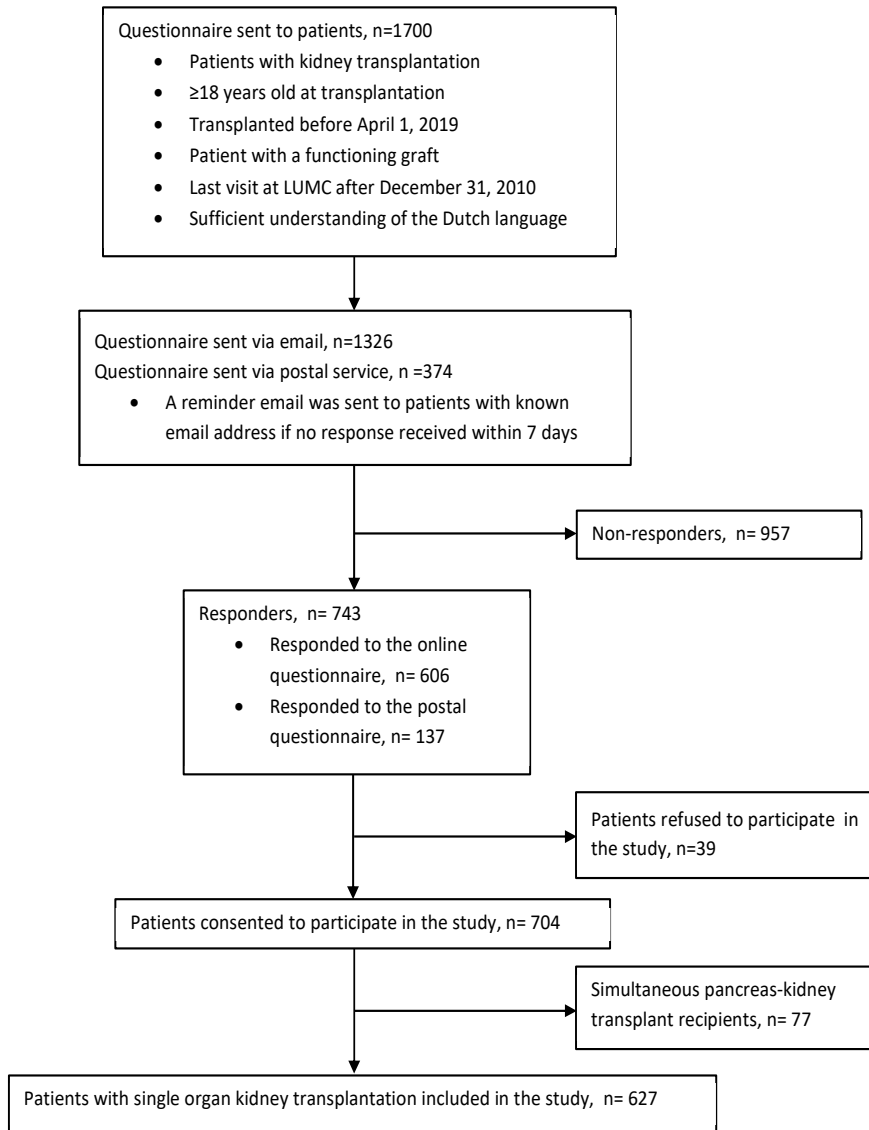
Figure 1. Flow chart of the study population

Table 1. *Patient characteristics of the total study population and stratified by post-transplant time categories..*

Characteristic	Total (n=627)	Post-transplant time		
		< 5yr (n=158)	5-15yr (n=312)	>15yr (n=157)
Mean age (SD) at study, yr	61.4 (11.3)	58.0 (11.9)	61.8 (11.5)	63.9 (9.3)
Age structure at study, n (%)				
18~39	31 (4.9)	14 (8.9)	15 (4.8)	2 (1.3)
40~59	233 (37.2)	68 (43.0)	114 (36.5)	51 (32.5)
60~79	350 (55.8)	76 (48.1)	176 (56.4)	98 (62.5)
80~	627 (2.1)	0 (0)	7 (2.2)	6 (3.8)
Mean (SD) age at KT, yr	50.0 (13.1)	54.9 (11.8)	52.5 (11.8)	40.0 (11.5)
Median (IQR) time after KT, yr	9.0 (10.2)	3.1 (1.8)	9.0 (4.8)	20.7 (11.3)
Female, n(%)	233 (37.2)	53 (33.5)	124 (39.7)	56 (35.7)
SES, n(%)[a]				
Low	64 (10.2)	22 (13.9)	26 (8.3)	16 (10.2)
Middle	397 (63.3)	101 (63.9)	200 (64.1)	96 (61.1)
High	161 (25.7)	34 (21.5)	83 (26.6)	44 (28.0)
Marital status, n(%)				
Single/separated	160 (25.5)	53 (33.5)	71 (22.8)	36 (22.9)
Married/living together	467 (74.5)	105 (66.5)	241 (77.2)	121 (77.1)
Education				
Low	52 (8.3)	12 (7.6)	22 (7.1)	18 (11.5)
Middle	215 (34.3)	52 (32.9)	107 (34.3)	56 (35.6)
High	360 (57.4)	94 (59.5)	183 (58.7)	83 (52.9)
Employment, n(%)				
Employed	291 (46.4)	83 (52.5)	142 (45.5)	66 (42.0)
Unemployed	69 (11.0)	24 (15.2)	32 (10.3)	13 (8.3)
Retired/Student	267 (42.6)	51 (32.3)	138 (44.2)	78 (49.7)
Primary Kidney Disease, n(%)[a]				
Congenital/hereditary kidney disease	15 (2.4)	0 (0)	8 (2.6)	7 (4.5)
Cystic kidney disease	139 (22.2)	38 (24.1)	78 (25.0)	23 (14.6)
Diabetes	33 (5.3)	21 (13.3)	12 (3.8)	0 (0)
Glomerulonephritis	136 (21.7)	34 (21.5)	75 (24.0)	27 (17.2)
Interstitial nephritis/pyelonephritis	51 (8.1)	11 (7.0)	21 (6.7)	19 (12.1)
Renal vascular disease	61 (9.7)	18 (11.4)	31 (9.9)	12 (7.6)
Other diseases	45 (7.2)	11 (7.0)	27 (8.7)	7 (4.5)
Unknown	102 (16.3)	24 (15.2)	51 (16.3)	27 (17.2)
Number of KTs, n(%)[a]				
1	540 (86.1)	133 (84.2)	263 (84.3)	144 (91.7)
>1	77 (12.3)	24 (15.2)	40 (12.8)	13 (8.3)
Donor type, n(%)[a]				
Living donor	376 (60.0)	102 (64.6)	212 (67.9)	62 (39.5)
Deceased donor	241 (38.4)	55 (34.8)	91 (29.2)	95 (60.5)
Mean (SD) BMI, kg/m^2 [a]	26.2 (4.6)	26.6 (4.5)	25.7 (4.3)	27.0 (5.4)
Comorbidities, n(%)[a]				
Diabetes Mellitus	97 (15.5)	31 (19.6)	47 (15.1)	19 (12.1)
Cardiovascular event	169 (27.0)	53 (33.5)	67 (21.5)	49 (31.2)
Cerebrovascular event	42 (6.7)	12 (7.6)	23 (7.4)	7 (4.5)
Immunosuppressants, n(%)[a]				
Prednisone	556 (88.7)	148 (93.7)	281 (90.1)	127 (80.9)
Tacrolimus	348 (55.5)	123 (77.8)	193 (61.9)	32 (20.4)
Mycophenolic acid	361 (57.6)	120 (75.9)	182 (58.3)	59 (37.6)

Data are presented as mean (SD) or median (IQR) for continuous variables and n (%) for categorical variables. Abbreviations: BMI, body mass index; IQR, interquartile range; KT, kidney transplantation; SES, socioeconomic status; SD, standard deviation.
[a] Variables with missing values: SES (0.8%), primary kidney disease (7.2%), number of KT (1.6%), donor type (1.6%), BMI (22.2%), diabetes (42.6%), cardiovascular event (39.1%), cerebrovascular event (47.8%), immunosuppressants (3.2%).

Illness perceptions

Mean (SD) scores of each illness perception are presented in **Table 3**. In general, the included KTRs believed to a relatively high extent that they understand their kidney disease (*illness coherence*) and that their kidney disease is a life-long chronic condition (*timeline*). They also had a strong belief that their treatment can control their disease (*treatment control*). The perceived *personal control* over their disease was lower than the perceived *treatment control* but could still be considered relatively high. The mean scores of the other illness perceptions laid around the midpoint of the scale (range: 3.8 to 5.0 on an 11-point scale ranging from 0 to 10), indicating that KTRs believed to a moderate extent that their kidney disease is a cause for concern (*concern*), has negative consequences upon their lives (*consequences*) and causes negative feelings (*emotional response*) and a high symptom burden (*illness identity*). After stratification, the results showed that KTRs with a longer post-transplant time believed to a lesser extent that their disease can be controlled by their treatment or by themselves (*treatment control* and *personal control*) and that they experienced a higher symptom burden due to kidney disease (*illness identity*).

Illness perceptions and non-adherence to immunosuppressants in KTRs

After adjusting for potential confounders, three illness perceptions (i.e. *illness identity*, *concern* and *illness coherence*) were significantly associated with non-adherence to immunosuppressants in KTRs. More specifically, the results showed that with one increment in scores on the illness perceptions *illness identity*, *concern* and *illness coherence*, the risk of non-adherence increased by 7%, 7% and 11%, respectively (**Table 4**). For the other five domains (i.e. *consequences*, *timeline*, *personal control*, *treatment control* and *emotional response*), the point estimates ranged from 1.02 to 1.05, indicating an association between less favorable illness perceptions of these illness perceptions and an increased risk of medication non-adherence but with wider confidence intervals. **Table 4** also shows the increased risk of medication non-adherence with every two increments in illness perception scores. None of the interactions between the separate illness perceptions and time after kidney transplantation were statistically significant (p-values ranged from 0.48 to 0.96).

Table 2. Medication non-adherence in the total study population and stratified by categories of post-transplant time.

Medication non-adherence, n(%)	Total (n=627)	Post-transplant time			A "yes" to the question indicates
		< 5yr (n=158)	5-15yr (n=312)	>15yr (n=157)	
Medication non-adherence	203 (32.4)	43 (27.2)	105 (33.7)	55 (35.0)	non-adherence to immunusuppressants in general. [a]
Issues with taking	77 (12.3)	14 (8.8)	41 (13.1)	22 (14.0)	Not taken immunosuppressants some times in the past 4 weeks.
Once a month	68 (10.8)	13 (8.2)	36 (11.5)	19 (12.1)	
More than once a month	9 (1.5)	1 (0.6)	5 (1.6)	3 (1.9)	
Drug holiday	5 (0.8)	1(0.6)	2 (0.6)	2 (1.3)	Skipped several consecutive doses of immunosuppressants in the past 4 weeks.
Once a month	3 (0.5)	1 (0.6)	2 (0.6)	0 (0)	
More than once a month	2 (0.3)	0 (0)	0 (0)	2 (1.3)	
Timing	171 (27.3)	35 (22.1)	88 (28.1)	48 (30.6)	Taken immunosuppressants with more than 2 hours' time difference from the prescribed dosing time in the past 4 weeks.
Once a month	101 (16.1)	22 (13.9)	56 (17.9)	23 (14.6)	
More than once a month	70 (11.2)	13 (8.2)	32 (10.2)	25 (16.0)	
Dose reduction	2 (0.4)	0 (0)	1 (0.3)	1 (0.6)	Reduced the prescribed amount of immunosuppressants in the past 4 weeks.
Once a month	1 (0.2)	0 (0)	1 (0.3)	0 (0)	
More than once a month	1 (0.2)	0 (0)	0 (0)	1 (0.6)	

[a] Any "yes" to the four questions of the four adherence-domains indicates medication non-adherence in general.

Table 3. Illness perceptions of the total study population and stratified by categories of post-transplant time.

Illness perception, mean (SD)[a]	Total (n=627)	Post-transplant time			A higher score indicates patients believe to a greater extent that...
		< 5yr (n=158)	5-15yr (n=312)	>15yr (n=157)	
Consequences	5.0 (2.9)	5.2 (2.9)	4.8 (2.9)	5.0 (3.1)	...their kidney disease has more negative consequences upon their life.
Timeline	8.6 (2.7)	8.4 (2.9)	8.8 (2.6)	8.6 (2.7)	...their kidney disease lasts for a longer time.
Personal control	3.8 (2.6)	3.4 (2.5)	3.8 (2.6)	4.3 (2.8)	...their kidney disease cannot be effectively controlled by themselves.
Treatment control	2.2 (2.3)	1.7 (2.0)	2.2 (2.2)	2.7 (2.6)	...their kidney disease cannot be effectively controlled by their treatment.
Illness identity	4.2 (2.9)	3.8 (2.8)	4.2 (2.9)	4.7 (2.9)	...their kidney disease causes more symptoms.
Concern	4.7 (2.9)	4.7 (2.8)	4.7 (2.8)	4.9 (3.1)	...their kidney disease causes greater worries about their health.
Illness coherence	1.6 (1.9)	1.7 (2.0)	1.3 (1.6)	1.9 (2.3)	...they do not understand their kidney disease.
Emotional response	3.8 (2.9)	4.1 (3.1)	3.5 (2.9)	4.0 (2.9)	...their kidney disease causes more emotional distress.

[a] Illness perceptions were measured on an 11-point scale ranging from 0 to 10, with higher scores reflecting stronger negative perceptions of their condition. *Personal control, treatment control* and *illness coherence* were recoded so that a higher score on these perceptions also indicate stronger negative illness perceptions.

Table 4. Associations between illness perceptions and medication non-adherence (n=627).

Illness perceptions	Crude OR (95% CI)[b]	P-value	Adjusted OR (95% CI)[a,b] per one increment in illness perceptions	Adjusted OR (95% CI)[a,c] per two increments in illness perceptions	P-value	P-value for interaction[b] (post-transplant time * illness perceptions)
Consequences	1.02 (0.97, 1.08)	0.44	1.02 (0.95, 1.08)	1.03 (0.91, 1.16)	0.64	0.48
Timeline	1.04 (0.98, 1.11)	0.21	1.02 (0.96, 1.10)	1.05 (0.91, 1.20)	0.51	0.96
Personal control	1.05 (0.99, 1.12)	0.10	1.05 (0.99, 1.13)	1.11 (0.97, 1.27)	0.12	0.52
Treatment control	1.05 (0.98, 1.23)	0.18	1.05 (0.97, 1.14)	1.11 (0.95, 1.29)	0.20	0.57
Illness identity	1.05 (0.99, 1.11)	0.14	1.07 (1.00, 1.14)	1.14 (1.00, 1.29)	0.05[d]	0.62
Concern	1.06 (1.00, 1.13)	0.04	1.07 (1.00. 1.14)	1.14 (1.00, 1.29)	0.05[d]	0.73
Illness coherence	1.08 (0.99, 1.17)	0.10	1.11 (1.01, 1.22)	1.23 (1.03, 1.48)	0.03	0.69
Emotional response	1.04 (0.98, 1.10)	0.22	1.03 (0.97, 1.10)	1.07 (0.94, 1.21)	0.32	0.64

Abbreviation: BMI, body mass index; CI, confidence interval; OR, odds ratio; SES, socioeconomic status.

[a]The adjusted variables included age at the study, sex, SES rank, marital status, employment status, education level, primary kidney disease, comorbidities, BMI, donor type, time after kidney transplantation, the number of transplantations received, and immunosuppressants.

[b]OR of one increment in illness perception scores on an 11-point scale

[c]OR of every two increments in illness perception scores on an 11-point scale.

[d]P-value < 0.05, namely: 0.045 for both illness perceptions 'illness identity' and 'concern'.

Sensitivity analyses

When repeating the logistic regression analysis without comorbidities and BMI (**Table S2**), the results showed that, although the association between *illness identity* and *concern* and medication non-adherence became statistically insignificant, the ORs (95% CI) supported the results from the main analysis (i.e. *illness identity*: 1.06, 95% CI, 1.00 to 1.13, p=0.06; *concern*: 1.06, 95% CI, 1.00 to 1.13, p=0.06; *illness coherence*: 1.11, 95% CI, 1.02 to 1.22, p=0.02).

Discussion

Despite the improvements in nephrology care, adherence to immunosuppressants remains a challenge in KTRs. Our study detected non-adherence to immunosuppressants in a considerable proportion of prevalent Dutch KTRs and associations between negative illness perceptions and medication non-adherence to immunosuppressants.

The proportion of nonadherent KTRs in our study (32.4%) is similar to the results of a previous literature review, which also reported a high weighted mean prevalence (28%) of medication

non-adherence to immunosuppressants in KTRs[5]. However, the prevalence of medication non-adherence reported by different studies may not be directly comparable as their definition for medication non-adherence may differ. Regarding the non-adherence behavioral pattern: taking medication 2 hours beyond the recommended dosing time was the most prevalent nonadherent behavior in our study population (27.3%), followed by not taking their medication sporadically (12.3%). These findings are in line with other studies that also reported non-adherence behavioral patterns in KTRs[24, 25].

Furthermore, our results showed that stronger negative illness perceptions are associated with medication non-adherence to immunosuppressants in KTRs. More specifically, less understanding of kidney disease (*illness coherence*), greater worries about the kidney disease (*concern*), and experiencing more symptoms due to the kidney disease (*illness identity*) significantly increased the risk of medication non-adherence by 7%, 7% and 11% with one unit increment on a 0-to-10 scale in our Dutch KTRs population. Our findings are in line with the results described by Cossart et al. that nonadherent KTRs believed to a lesser extent that they understand their kidney disease (*illness coherence*)[12]. Additionally, our results indicated that the more worried patients were about their kidney disease (*concerns*), the more likely it was that they were nonadherent -- an association that has also been reported in patients after myocardial infarction[26]. A possible explanation for this finding is that highly concerned patients may have a more fatalistic attitude towards their disease (e.g. progression of their disease is inevitable) and are, therefore, less strict with their medication taking. Finally, our results showed that patients who attributed a greater symptom burden to their kidney disease were less adherent. This result is supported by findings reported by Rosenberger and colleagues[27] suggesting that KTRs with more adverse effects due to their chronic immunosuppressive treatment (e.g. tremor, diarrhea and fatigue) were more likely to be nonadherent. Of note, the results also suggested an association between less favorable illness perceptions of the other five domains (i.e. *consequences*, *timeline*, *personal control*, *treatment control* and *emotional response*) and increased risk of medication non-adherence despite statistical insignificance.

In general, the association between illness perceptions and medication non-adherence is consistent with Leventhals' CSM[6] and the results reported by others in patients with chronic conditions, such as hypertension and diabetes[28, 29]. However, we did not observe the discrepancy found in the study conducted by Massey and colleagues[13], namely that some illness perceptions (*consequence* and *emotional response*) became more favorable over time while medication non-adherence still increased. The different study populations and study design may explain such differences in findings: Massey and colleagues' population consisted of newly transplanted patients in a longitudinal study, while our study population was

prevalent patients in a cross-sectional study. Notably, we did not detect a difference in the relationships between illness perceptions and medication non-adherence in patients with different time after kidney transplantation; however, we cannot rule out the possibility that these insignificant results are due to the participation of healthier KTRs regardless of their post-transplant time. Future studies with a longitudinal design and sufficient length of follow-up are needed to test the association between illness perceptions and medication non-adherence over time.

Our study suggests a need to improve medication adherence to immunosuppressants in KTRs along with previous research[5], and also suggests that negative illness perceptions could be a potential interventional target to achieve this. In our analyses, a perceived lack of understanding of kidney disease (*illness coherence*) was most strongly associated with medication non-adherence among other illness perceptions. However, a lack of illness understanding among patients is not uncommon in clinical practice: two previous studies in a clinical setting found that only 42% and 77% of the patients were able to list their diagnosis and that 14% and 17% of the patients were able to state the common side effects of their medication[30, 31]. Such findings have shown adequate room to modify negative illness perceptions, which are indeed modifiable according to existing evidence in other patient groups and the CSM[6, 32-35]. Current interventions to improve illness perceptions are mainly derived from the CSM framework and usually involve behavior change techniques to modify the psychosocial determinants of unwanted (e.g. nonadherent) behavior, for instance: patient education, motivational interviewing, goal setting, identifying and solving problems, improving social support and facilitating support seeking[33, 34]. In recent years, attempts have also been made to introduce self-management support programmes into care for patients with chronic conditions on top of the conventional treatment by healthcare professionals[35]. Futures studies are needed to facilitate translation of such knowledge into practice by identifying the effects of different behavior change techniques to modify unhelpful illness perceptions, the efficient approaches to deliver such interventions to the patients, and the optimal logistics to implement such interventions into clinical practice. In addition to cognitive-behavioral interventions, our results also suggested that patients could benefit from active management of immunosuppressant-related side effects in KTRs. Future studies may also focus on identifying potential risk factors for unhelpful illness perception to tailor intervention. Finally, efforts are warranted to understand the clinically relevant level of occurrence and frequency of self-reported nonadherent behaviors in terms of the therapeutic effect of prescribed immunosuppressants to facilitate a more clinically relevant understanding of our results.

The strengths of this study include that our study population consists of KTRs covering a broad time span after kidney transplantation and that we are one of the first studies to examine the associations between illness perceptions and medication non-adherence in this specific population. Additionally, our analyses included relatively large sample size, especially compared to the previous studies investigating similar topics[12, 13]. Our study also has several limitations that should be taken into account. First, medication non-adherence was measured using self-report, which is prone to underestimate medication non-adherence[36]. This could have potentially introduced outcome misclassification bias, leading to underestimating the association between illness perceptions and medication non-adherence. Second, the responders may not be representative of the general Dutch KTRs; compared to the non-responders (**Table S1**), responders were more likely to be in a better SES, receive living donor kidney transplantation and were less likely to have diabetes as PKD. A previous survey study also suggests that responders better adhere to their medication regime than non-responders[37]. Such differences between responders and non-responders could influence the generalizability of our results. Moreover, the majority of our study population was between 40 and 80 years old, which could lead to compromised generalizability of our results in young KTRs. Third, our study was conducted in prevalent Dutch KTRs, and thus, future studies are needed to investigate whether our results can be generalized to different populations. Finally, due to our observational cross-sectional design, residual confounding as a result of unmeasured confounders (e.g. pill burden) exists and causal interpretation is limited, although the theoretical fundaments of CSM are considered quite robust[6, 38].

In conclusion, this study suggests that stronger negative illness perceptions are associated with medication non-adherence to immunosuppressants in KTRs. The high prevalence of medication non-adherence in our study indicates room for improvement and that KTRs need additional support to adhere to this strict medication regime. Targeting negative illness perceptions utilizing psychoeducational interventions could possibly optimize medication adherence and consequently improve health outcomes in KTRs. Future studies are needed to explore such interventions' effects and identify facilitators and barriers for implementing such support strategies to help its uptake in clinical practice.

References

1. Knight SR. Routine adherence monitoring after renal transplantation. *Transpl Int*. 2019; **32**: 600-2.

2. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation*. 2004; **77**: 769-76.

3. Prihodova L, Nagyova I, Rosenberger J, et al. Adherence in patients in the first year after kidney transplantation and its impact on graft loss and mortality: a cross-sectional and prospective study. *J Adv Nurs*. 2014; **70**: 2871-83.

4. Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant*. 2009; **9**: 2597-606.

5. Denhaerynck K, Dobbels F, Cleemput I, et al. Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. *Transpl Int*. 2005; **18**: 1121-33.

6. Leventhal H, Steele D. Illness Representations and Coping with Health Threats. *Handbook of psychology and health volume IV social psychology aspects of health*. 1984; **4**.

7. Meuleman Y, de Goeij MC, Halbesma N, Chilcot J, Dekker FW, van Dijk S. Illness Perceptions in Patients on Predialysis Care: Associations With Time Until Start of Dialysis and Decline of Kidney Function. *Psychosomatic medicine*. 2015; **77**: 946-54.

8. Serlachius A, Gamble G, House M, et al. Illness Perceptions and Mortality in Patients With Gout: A Prospective Observational Study. *Arthritis care & research*. 2017; **69**: 1444-8.

9. Thong MS, Kaptein AA, Vissers PA, Vreugdenhil G, van de Poll-Franse LV. Illness perceptions are associated with mortality among 1552 colorectal cancer survivors: a study from the population-based PROFILES registry. *Journal of cancer survivorship : research and practice*. 2016; **10**: 898-905.

10. Meuleman Y, Chilcot J, Dekker FW, Halbesma N, van Dijk S. Health-related quality of life trajectories during predialysis care and associated illness perceptions. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association*. 2017; **36**: 1083-91.

11. Kucukarslan SN. A review of published studies of patients' illness perceptions and medication adherence: Lessons learned and future directions. *Research in Social and Administrative Pharmacy*. 2012; **8**: 371-82.

12. Cossart AR, Staatz CE, Campbell SB, Isbel NM, Cottrell WN. Investigating barriers to immunosuppressant medication adherence in renal transplant patients. *Nephrology (Carlton)*. 2019; **24**: 102-10.

13. Massey EK, Tielen M, Laging M, et al. Discrepancies Between Beliefs and Behavior: A Prospective Study Into Immunosuppressive Medication Adherence After Kidney Transplantation. *Transplantation*. 2015; **99**: 375-80.

14. Loghman-Adham M. Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. *Am J Manag Care*. 2003; **9**: 155-71.

15. McAndrew LM, Musumeci-Szabó TJ, Mora PA, et al. Using the common sense model to design interventions for the prevention and management of chronic illness threats: From description to process. *British Journal of Health Psychology*. 2008; **13**: 195-204.

16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008; **61**: 344-9.

17. Central Committee on Research Involving Human Subjects. https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research. Accessed May 10, 2021.

18. Neuberger JM, Bechstein WO, Kuypers DR, et al. Practical Recommendations for Long-term Management of Modifiable Risks in Kidney and Liver Transplant Recipients: A Guidance Report and Clinical Checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. *Transplantation*. 2017; **101**: S1-s56.

19. De Geest S, Zullig LL, Dunbar-Jacob J, et al. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). *Annals of internal medicine*. 2018; **169**: 30-5.

20. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res*. 2006; **60**: 631-7.

21. SCP Statusscores (2016). http://www.scp.nl/Formulieren/Statusscores_opvragen. Accessed March 03, 2019. .

22. Hemke AC, Heemskerk MB, van Diepen M, Weimar W, Dekker FW, Hoitsma AJ. Survival prognosis after the start of a renal replacement therapy in the Netherlands: a retrospective cohort study. *BMC Nephrol*. 2013; **14**: 258.

23. Royston P. Multiple imputation of missing values. *The Stata Journal*. 2004; **4**: 227-41.

24. Lennerling A, Forsberg A. Self-reported non-adherence and beliefs about medication in a Swedish kidney transplant population. *Open Nurs J*. 2012; **6**: 41-6.

25. Abedini S, Gøransson L, Cockburn E, Kilany S, Holdaas H. Immunosuppression Adherence in Stable Kidney Transplant Patients Converted From Immediate- to Prolonged-Release Tacrolimus in Clinical Practice: A Norwegian Study. *Transplant Direct*. 2018; **4**: e338.

26. Crowley MJ, Zullig LL, Shah BR, et al. Medication non-adherence after myocardial infarction: an exploration of modifying factors. *J Gen Intern Med*. 2015; **30**: 83-90.

27. Rosenberger J, Geckova AM, van Dijk JP, et al. Prevalence and characteristics of noncompliant behaviour and its risk factors in kidney transplant recipients. *Transpl Int*. 2005; **18**: 1072-8.

28. Chen SL, Tsai JC, Lee WL. The impact of illness perception on adherence to therapeutic regimens of patients with hypertension in Taiwan. *J Clin Nurs*. 2009; **18**: 2234-44.

29. Broadbent E, Donkin L, Stroh JC. Illness and treatment perceptions are associated with adherence to medications, diet, and exercise in diabetic patients. *Diabetes Care*. 2011; **34**: 338-40.

30. Nicholson Thomas E, Edwards L, McArdle P. Knowledge is Power. A quality improvement project to increase patient understanding of their hospital stay. *BMJ Qual Improv Rep*. 2017; **6**.

31. Makaryus AN, Friedman EA. Patients' understanding of their treatment plans and diagnosis at discharge. *Mayo Clin Proc*. 2005; **80**: 991-4.

32. Rakhshan M, Rahimi M, Zarshenas L. The Effect of an Education Program Based on Illness Perception on the Lifestyle of Patients with Metabolic Syndrome: A Randomized Controlled Clinical Trial. *Int J Community Based Nurs Midwifery*. 2019; **7**: 279-87.

33. Alyami M, Serlachius A, O'Donovan CE, van der Werf B, Broadbent E. A systematic review of illness perception interventions in type 2 diabetes: Effects on glycaemic control and illness perceptions. *Diabet Med*. 2021; **38**: e14495.

34. Easthall C, Song F, Bhattacharya D. A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence. *BMJ Open*. 2013; **3**.

35. Dobson R, Whittaker R, Jiang Y, et al. Effectiveness of text message based, diabetes self management support programme (SMS4BG): two arm, parallel randomised controlled trial. *BMJ (Clinical research ed)*. 2018; **361**: k1959.

36. Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: A systematic review. *BMC Medical Research Methodology*. 2011; **11**: 149.

37. Gadkari AS, Pedan A, Gowda N, McHorney CA. Survey nonresponders to a medication-beliefs survey have worse adherence and persistence to chronic medications compared with survey responders. *Med Care*. 2011; **49**: 956-61.

38. Hagger MS, Koch S, Chatzisarantis NLD, Orbell S. The common sense model of self-regulation: Meta-analysis and test of a process model. *Psychological bulletin*. 2017; **143**: 1117-54.

Supplementary files

Supplementary Table S1. Patient characteristics of responders and non-responders (n=1449).

Supplementary Table S2. Associations between illness perceptions and medication non-adherence without adjusting for comorbidity and BMI (n=627).

Table S1. Patient characteristics of responders and non-responders (n=1449).

Characteristic	Responders (n=627)	Non-responders (n=822)
Mean age at study (SD), yr	61.4 (11.3)	58.3 (13.7)
Mean age at KT (SD), yr	50.0 (13.1)	48.0 (14.1)
Median time after KT (IQR), yr	9.0 (10.2)	7.9 (8.4)
Female, n (%)	233 (37.2)	316 (38.4)
SES rank, n (%)[a]		
Low	64 (10.2)	188 (22.9)
Middle	397 (63.3)	481 (58.5)
High	161 (25.7)	138 (17.1)
Primary kidney disease, n(%)[a]		
Congenital/hereditary kidney disease	15 (2.4)	43 (5.2)
Cystic kidney disease	139 (22.2)	106 (12.9)
Diabetes Mellitus	33 (5.3)	99 (12.0)
Glomerulonephritis	136 (21.7)	189 (23.0)
Interstitial nephritis/pyelonephritis	51 (8.1)	72 (8.8)
Renal vascular disease	61 (9.7)	72 (8.8)
Other diseases	45 (7.2)	58 (7.1)
Unknown	102 (16.3)	145 (17.6)
Number of Tx, n(%)[a]		
1	540 (86.1)	717 (87.2)
>1	77 (12.3)	102 (12.4)
Donor type, n(%)[a]		
Living donor	376 (60.0)	433 (52.7)
Deceased donor	241 (38.4)	386 (47.0)
Mean BMI (SD), kg/m²[a]	26.2 (4.6)	26.5 (4.7)
Comorbidities, n(%)[a]		
Diabetes Mellitus	97 (15.5)	114 (13.9)
Cardiovascular event	169 (27.0)	182 (22.1)
Cerebrovascular event	42 (6.7)	51 (6.2)
Immunosuppressants, n(%)[a]		
Prednisone	556 (88.7)	740 (90.0)
Tacrolimus	348 (55.5)	447 (54.4)
Mycophenolic acid	361 (57.6)	494 (60.1)

Data are presented as mean (SD) or median (IQR) for continuous variables and n (%) for categorical variables.
Abbreviation: BMI, body mass index; IQR, interquartile range; KT, kidney transplantation; SES, socioeconomic status; SD, standard deviation.
[a]Variables with missing values: SES rank (0.8% and 1.8%), primary kidney disease (7.2% and 4.6%), number of transplantation (1.6% and 0.4%), donor type (1.6% and 0.4%), BMI (22.2% and 20.1%), diabetes (42.6% and 37.5%), cardiovascular event (39.1% and 37.3%), cerebrovascular event (47.8% and 42.6%) and immunosuppressants (3.2% and 3.4%) for responders and non-responders, respectively.

Table S2. Associations between illness perceptions and medication non-adherence without adjusting for comorbidity and BMI (n=627).

Illness perceptions	Crude OR (95% CI)[b]	P-value	Adjusted OR (95% CI)[a,b]	P-value	P-value for interaction[b] (post-transplant time * illness perceptions)
Consequences	1.02 (0.97, 1.08)	0.44	1.01 (0.95, 1.08)	0.69	0.49
Timeline	1.04 (0.98, 1.11)	0.21	1.02 (0.95, 1.09)	0.59	0.94
Personal control	1.05 (0.99, 1.12)	0.10	1.06 (0.99, 1.13)	0.10	0.59
Treatment control	1.05 (0.98, 1.23)	0.18	1.06 (0.98, 1.14)	0.15	0.59
Illness identity	1.05 (0.99, 1.11)	0.14	1.06 (1.00, 1.13)	0.06	0.59
Concern	1.06 (1.00, 1.13)	0.04	1.06 (1.00. 1.13)	0.06	0.76
Illness coherence	1.08 (0.99, 1.17)	0.10	1.11 (1.02, 1.22)	0.02	0.62
Emotional response	1.04 (0.98, 1.10)	0.22	1.03 (0.97, 1.09)	0.35	0.66

Abbreviation: BMI, body mass index; CI, confidence interval; OR, odds ratio; SES, socioeconomic status.
[a]The adjusted variables included age at study participation, sex, SES rank, marital status, employment status, education level, primary kidney disease, donor type, time after kidney transplantation, the number of transplantations received, and immunosuppressants.
[b]OR of one increment in illness perception scores on an 11-point scale.