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Objectives. To explore whether distinct trajectories of anxiety and depression exist among liver transplant candidates, and to gain insight into demographic, clinical, and individual characteristics related with these trajectories.

Design. A multicentre, prospective cohort study among 216 liver transplant candidates. Respondents filled out a questionnaire at study entrance and subsequently every 6 months until transplantation or removal from the waiting list.

Methods. Anxiety (STAI6), depression (CES-D), demographic, and individual variables were assessed by questionnaire. Clinical variables were retrieved by medical record review. The SAS PROC TRAJ procedure was used to identify distinct trajectories. Univariate and multiple ordinal logistic regression analyses were used to explore related variables.

Results. Regarding anxiety, three stable trajectories were identified as follows: below clinical level (51%), slightly above clinical level (34%), and high above clinical level (15%). Regarding depression, four stable trajectories were identified as follows: below clinical level (23%), slightly below clinical level (34%), slightly above clinical level (28%), and high above clinical level (6%). For anxiety as well as for depression, experiencing more liver disease symptoms, a lower level of personal control, making more use of emotional coping, and making less use of task-oriented coping increased the likelihood of membership in those trajectories with higher symptom levels.

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> **Conclusion.** Distinct, but stable, trajectories of anxiety and depression were present in liver transplant candidates. The trajectories with symptom levels above clinical relevant levels for anxiety or depression comprised, respectively, 49% and 34% of the respondents. Therefore, psychological screening and subsequently providing appropriate interventions are warranted early in the transplant process.

Statement of contribution

What is already known on this subject
- For transplant candidates, the waiting-list period is a period of uncertainty and unpredictability.
- Psychological problems, such as anxiety and depression, are common among liver transplant candidates.
- Several demographic, clinical, and individual characteristics are associated with anxiety and depression, but these results remain inconclusive.

What does this study add
- Distinct trajectories of symptoms of anxiety and depression are present among liver transplant candidates.
- Given the stability of the trajectories over time, the symptom level at baseline is indicative of the symptom level during the waiting-list period.
- Experiencing more liver disease symptoms, low mastery, more use of emotional coping, and less use of task-oriented coping are associated with trajectories of high symptom levels.

In the Eurotransplant region, over 2,000 patients with end-stage liver disease are waiting for a liver transplant, while about 1,600 patients per year receive a liver transplant (Eurotransplant International Foundation, 2015). More specifically, in the Netherlands, about 200 patients are placed on the waiting list for a liver transplant per year, while approximately 145 patients receive a liver transplant (Dutch Transplantation Society, 2015). Due to the gap between supply and demand for organ donors, transplant candidates may have to wait for a donor offer for a prolonged period of time. Each year approximately 15% of transplant candidates die while on the organ transplant waiting list (Dutch Transplantation Society, 2015).

Waiting for a new organ puts much stress on patients. Not only are they confronted with deterioration in their physical health but they also have to deal with uncertainty – will the transplant come in time – and unpredictability – when will the transplant take place (Haugh & Salyer, 2007; Martin, Stone, Scott, & Brashers, 2010; Moran, Scott, & Darbyshire, 2011; Toimamueang *et al.*, 2003). Although the prospect of a transplantation offers new hope for the future, transplant candidates often feel that their life is on hold (Moran *et al.*, 2011; Rosenberger, Dew, DiMartini, DeVito Dabbs, & Yusen, 2012).

Given the stressors encountered by transplant candidates, it is not surprising that psychological problems, such as anxiety and depression, are common during the waiting-list period. Among liver transplant candidates, prevalence rates of 14–52% regarding anxiety (Gutteling, de Man, Busschbach, & Darlington, 2007; Lopez-Navas *et al.*, 2011; Miller *et al.*, 2013; Russell, Feurer, Wisawatapnimit, Salomon, & Pinson, 2008; Stewart, Hart, Gibson, & Fisher, 2014) and of 17–60% regarding depression (Guimaro, Lacerda, Karam, Ferraz-Neto, & Andreoli, 2008; Gutteling *et al.*, 2007; Lopez-Navas *et al.*, 2011; Miller *et al.*, 2013; Russell *et al.*, 2008; Stewart *et al.*, 2014) have been described. These prevalence rates vary widely because of differences in screening instruments and cut-off scores used.

Psychological problems before transplantation have been associated with poor psychological health after transplantation (Caccamo *et al.*, 2001; Miller *et al.*, 2013; Rogal, Landsittel, Surman, Chung, & Rutherford, 2011), which in turn has been associated

with poorer outcomes after transplantation regarding adherence (Chiu, Chen, & Cheng, 2009; Errichiello, Picozzi, & de Notaris, 2014), quality of life (Errichiello *et al.*, 2014; Kugler *et al.*, 2013; Miller *et al.*, 2013), and mortality (Corruble *et al.*, 2011; Rogal, Dew, Fontes, & DiMartini, 2013). Therefore, effective treatment of symptoms of anxiety and depression during the waiting-list period may contribute to an optimal preparation for transplantation and better outcomes after transplantation.

So far, little is known about the evolution of symptoms of anxiety and depression during the waiting-list period, because most studies describing prevalence rates of anxiety and depression have a cross-sectional design, and data are often assessed before or shortly after placement on the waiting list. Regarding liver transplant candidates, two studies have described the course of symptoms of depression and anxiety as remaining stable during the first 6 months after placement on the waiting list (Goetzmann *et al.*, 2006; Malik *et al.*, 2014). Three studies among lung, heart, and kidney transplant candidates revealed an increase in symptoms of anxiety and depression over time during the waiting-list period (Corruble *et al.*, 2010; Vermeulen, Bosma, van der Bij, Koeter, & Ten Vergert, 2005; Zipfel *et al.*, 1998). However, these studies examined the course of symptoms of anxiety and depression on a group level. Distinct trajectories, representing clusters of individual developmental courses for symptoms of anxiety and depression during the waiting-list period, have not been examined yet. Thus, we do not know whether transplant candidates become increasingly anxious over time, or whether transplant candidates who are already depressed remain depressed.

Most studies describing on trajectories of anxiety and depression in other chronic illness patient groups (Ng, Tan, Mooppil, Newman, & Griva, 2015; Yohannes *et al.*, 2016) or in cancer patients during medical treatment (Henselmans *et al.*, 2010; Lam *et al.*, 2013) distinguished four distinct patterns: chronic low symptom levels, chronic high symptom levels, increasing symptom levels, and decreasing symptom levels. In most studies, the majority of respondents (50–68%) showed chronic low symptoms levels, whereas a minority (9–24%) showed chronic high symptom levels, and 20–30% showed fluctuating symptom levels. Based on these results, it might be hypothesized that the majority of the transplant candidates will show low symptom levels of anxiety and depression over time and that only a minority will show high symptom levels over time. Besides this, a significant subset of transplant recipients may show an increase in symptom level over time due to the deterioration in health status and an increase in feelings of uncertainty.

In addition, insight into the demographic, clinical, and individual characteristics that distinguish the distinct trajectories of symptoms of anxiety and depression can provide health care workers with valuable insights for interventions aimed at reducing distress during the waiting-list period. In the literature, several variables have been related with higher levels of anxiety and/or depression in transplant candidates. These include demographic characteristics, such as age, sex, marital status, and employment status (Corruble *et al.*, 2011; Lopez-Navas *et al.*, 2011; Sainz-Barriga *et al.*, 2005; Santos *et al.*, 2010); clinical characteristics, such as the Model for End-stage Liver Disease (MELD) score; time on the waiting list; and perceived health status (Gutteling *et al.*, 2007; Martin-Rodriguez, Perez-San-Gregorio, Dominguez-Cabello, Fernandez-Jimenez, & Perez Bernal, 2012; Rogal *et al.*, 2011) and individual characteristics, such as coping style, personal control, social support, and self-efficacy (Dew *et al.*, 1994; Gutteling *et al.*, 2007; Lopez-Navas *et al.*, 2011). However, other studies have shown contradictory results regarding these factors (Martins, Sankarankutty, Silva, & Gorayeb, 2006; Ye *et al.*, 2013). Although these variables are related with higher levels of anxiety and depression measured on a

group level, we have to rely on these studies to identify possible predictors for distinct trajectories, because studies on distinct trajectories are lacking.

Therefore, the aim of this study was to explore whether distinct trajectories of anxiety and depression are present in liver transplant candidates, how these trajectories evolve over time, and to identify which demographic, clinical, and individual characteristics are related with these trajectories.

Materials and methods

This study was part of a prospective cohort study on psychological aspects of liver transplantation among transplant patients of three liver transplant centres in the Netherlands. All transplant candidates on the waiting list between October 2009 and April 2013 were eligible to participate if they were 18 years or older, and received pre-transplant care in one of the transplant centres. Exclusion criteria were as follows: not being able to fill out a questionnaire due to physical, mental, or cognitive functioning, or a language barrier.

Informed consent was obtained from all the individual participants included in the study. After written informed consent, respondents received a baseline questionnaire (T0), which they were asked to fill out within 2 weeks. A reminder was sent after 2 weeks, if necessary. The measurement of symptoms of anxiety and depression was repeated every 6 months (T1–T7) after inclusion in the study until either transplantation, removal from the waiting list, death during the waiting-list period, or the end of the study in October 2013.

The institutional review board of the transplant centre that initiated the study approved the study, and a positive recommendation of local feasibility was obtained from the other transplant centres (METc2009.190).

Measurements

Outcome variables

The outcome variables of anxiety and depression were included in the questionnaire at all measurement points.

Symptoms of anxiety were measured using the short form of the State-Trait Anxiety Inventory (STAI-6) (Marteau & Bekker, 1992). The STAI-6 consists of six items rated on a 4-point intensity scale (from 1 = not at all to 4 = very much), resulting in a total sum score between 6 and 24. Higher scores indicate more symptoms of anxiety. Based on a transformation of the original 20-item scale cut-off of ≥40 for the general population (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), a cut-off score of ≥12 was used to identify clinically relevant cases. The convergent validity of the STAI-6, with the full form of the STAI, showed a correlation of .95 (Van der Bij, De Weerd, Cikot, Steegers, & Braspenning, 2003). Cronbach's α of the STAI-6 in this study varied from .75 to .88 at the different measurement points.

Symptoms of depression were assessed using the Dutch version of the Center for Epidemiological Studies Depression scale (CES-D) (Bouma, Ranchor, Sanderman, & Van Sonderen, 1995). The CES-D consists of 20 items, scored on a 4-point self-report scale (from 0 = seldom or never to 4 = most of the time/always). Higher scores indicate more symptoms of depression. A cut-off score of ≥16 was used to identify clinically relevant

cases (Radloff, 1977). Cronbach's α of the CES-D in this study varied from .79 to .94 at the different measurement points.

Predictor variables
All predictor variables were measured once at the baseline measurement (T0).

Demographic characteristics regarding age, sex, marital status, educational level, and employment status were retrieved by self-report.

Clinical characteristics regarding primary liver disease, presence of hepatocellular carcinoma (HCC), time since diagnosis, time on waiting list, MELD score at time of listing, number of comorbidities, and the severity of liver disease symptoms were examined. Most of the variables were retrieved by medical record review. To measure comorbidity and liver disease symptoms, two research instruments were included in the questionnaire:

1. To measure comorbidities, a checklist of twenty common medical problems adapted from the health survey of the Dutch central statistics office, Statistics Netherlands, was used (www.cbs.nl; accessed 01/15/2015). This checklist included common medical conditions such as pulmonary diseases, heart diseases, stroke, gastrointestinal disorders, kidney function disorder, diabetes mellitus, joint complaints, and cancer. Respondents were asked to indicate which medical conditions, in addition to the liver disease, they had (yes/no), and whether they had received treatment (yes/no) for any of these medical conditions in the past 12 months. The total number of comorbidities was calculated by adding up all medical conditions for which treatment was received in the past year. Previous studies suggest that this method of self-reported comorbidity tends to be an accurate representation of actual comorbidity (Kriegsman, Penninx, van Eijk, Boeke, & Deeg, 1996; Van den Bos, 1995). Moreover, it has been found to be applicable in a transplant population (Schulz *et al.*, 2013).

2. The Liver Disease Symptom Index 2.0 (LDSI) (Van der Plas *et al.*, 2004) was used to measure the severity of specific liver disease symptoms. The LDSI includes 18 items, of which nine measure the severity of liver disease-related symptoms, such as itch, jaundice, and sleepiness during the day. The other nine items measure the hindrance caused by these symptoms in terms of daily activities. All items are scored on a 5-point Likert scale ranging from 'not at all' (0) to 'to a great extent' (4). The LSDI has shown good feasibility and good test–retest reliability (Van der Plas *et al.*, 2004). Two items, regarding depressive and anxious feelings, were removed from the analyses to avoid overlap with the outcome variables. In this study, only the severity scale of the LDSI was used. This score was calculated by summing up the scores of the remaining items.

Regarding *individual characteristics*, the level of personal control and coping style used were taken into account, because these are modifiable factors. In addition to these characteristics, the number of life events was examined as a potential confounder variable.

1. *Personal control,* the general perception of control over life, was measured using the Pearlin-Schooler Mastery Scale (Pearlin & Schooler, 1978). The Mastery Scale measures the degree to which individuals feel they can control things that happen to them, and it consists of seven items rated on a 5-point Likert scale (1 = totally disagree, 5 = totally agree). Total scores range from 7 (low personal control) to 35 (high personal control). The Mastery Scale is used in a variety of well and ill

populations and has shown good reliability and validity (Pearlin & Schooler, 1978). Cronbach's α in this study was .80.

2. *Coping style* was measured using the short form of the Coping Inventory for Stressful Situations (CISS-SF). The CISS-SF measures three dimensions of responses to stressful circumstances: task-oriented, emotional, and avoidance coping. The CISS-SF consists of 21 items, where respondents can rate the extent to which they engage in various types of coping activities, when confronted with stressful situations, on a 5-point Likert scale (from 1 = not at all to 5 = very much) (Cohan, Jang, & Stein, 2006). Higher scores on a subscale indicate more use of the specific coping style. In this study, the Cronbach's α of the subscales were as follows: .79 for the task-oriented coping scale, .82 for the emotional coping scale, and .78 for the avoidance coping scale.

3. Other *Stressful life events,* in addition to having end-stage liver disease, which may influence a person's life and psychological functioning, were measured using the Trauma and Life Event Self-report Inventory (TLESI) (Hovens, Bramsen, van der Ploeg, & Reuling, 2000). The TLESI consists of a list of eleven stressful events, where a person can indicate which events happened in the past 5 years. Additional life events that had an influence on a person's life could be added. In the analyses, the number of reported life events was taken into account.

Data analyses

Distinct trajectories were identified using PROC TRAJ in SAS 9.4 (SAS Institute Inc., Cary, NC, USA), a group-based modelling strategy for analysing developmental trajectories over age or time. PROC TRAJ identifies latent clusters of individuals following a similar course of development and is able to identify time trajectories of maximally third-order polynomials in a population. Respondents are assigned to one of the identified trajectories by calculating the probability of membership in each latent cluster for each respondent using a censored normal mixture model (Jones, Nagin, & Roeder, 2001). This means that the response variables (anxiety and depression) are normally distributed within each trajectory.

To select the best model, several criteria were used as follows: (1) The Bayesian information criterion (BIC) and the Akaike information criterion (AIC) were used to measure the relative fit of the model, with lower values indicating a better fit; (2) the posterior probabilities of group membership, the estimated probability of group membership for individuals assigned to each group, should exceed a minimum threshold of 0.7; and (3) an extra class of substantial size (>5%) should be conceptually meaningful and represent a trajectory differing from trajectories with fewer classes (Nagin & Odgers, 2010).

The waiting-list cohort was a dynamic cohort; subjects were being continuously enrolled in or removed from the waiting-list group (in case of transplantation, removal from the waiting list, or death) during the follow-up period. Therefore, the number of observations for each transplant candidate and the sample sizes per measurement point varied between one and eight measurements. However, PROC TRAJ can handle missing data of the type Missing at Random (MAR) and Missing Not at Random (MNAR) using maximum-likelihood estimation. To check the robustness of our findings, sensitivity analyses were performed using data from five of the eight measurements points (T0–T4).

Cluster membership with respect to the trajectories of anxiety and depression, identified for each transplant candidate, was added to an IBM SPSS Statistics 22.0 database (SPSS Inc., Chicago, 2013), which was used for all other analyses. Descriptive statistics were used to calculate the mean scores or prevalence rates of the demographic, clinical, and individual characteristics. Univariate ordinal logistic regression (OLR) analysis was used to examine whether these characteristics were significantly related with the distinct trajectories. Characteristics that were significantly related with trajectories were entered into a multiple OLR analysis to examine the independent effect of these characteristics on the distinct trajectories using odds ratios.

To test the stability of the trajectories over time, the effect size of partial eta squared (η_p^2) was used. Partial eta squared describes the proportion of the total variability attributable to a factor (Levine & Hullett, 2002). GLM repeated-measures ANOVA with time as a factor was used to calculate η_p^2. Because of the small sample sizes in the measurement points T5–T7, these analyses were performed using the data of the measurement points T0–T4. p-value was set at .05, two-tailed, for all analyses.

Results

Of the 474 liver transplant candidates on the waiting list between October 2009 and April 2013, 350 were eligible to participate in the study (Figure 1). Of these, 241 liver transplant candidates (68.9%) agreed to participate. Liver transplant candidates not willing to participate were significantly younger (48.0 years, ±13.6; p = .02) than those willing to participate. Besides this, candidates with the primary diagnosis of biliary cirrhosis were more willing to participate (76%, p = .048), whereas candidates within the group of miscellaneous diseases were less willing to participate (54%, p = .03). Regarding sex, time since diagnosis, time on waiting list, and MELD score, no differences were found between participants and non-participants.

Two hundred and sixteen liver transplant candidates (93.1%) responded to the baseline questionnaire (T0); 25 did not return the baseline questionnaire for several reasons (Figure 1).

During the study period, 116 of the respondents received a transplant (53.7%), 15 respondents (6.9%) were removed from the waiting list, and 14 respondents (6.5%) died during the waiting-list period (Figure 1). At the end of the study, 71 respondents were still on the waiting list.

Demographic, clinical, and individual characteristics of the study population are presented in Table 1.

Trajectories of anxiety during the waiting-list period
The parameter estimates of the trajectory analysis showed that the model identifying three distinct trajectories was the best model for symptoms of anxiety (Table 2). In this model, the BIC score was the lowest, posterior probabilities exceeded the threshold of >0.7, and all trajectories comprised >5% of the study population. In Figure 2, the distinct trajectories of anxiety are depicted, in which the dotted line represents the predicted values of the cluster-specific trajectories, and the solid line, the observed average values. The three distinctive trajectories of anxiety were characterized by the following: (1) a group with average symptom scores below the clinical level, comprising 51.3% (n = 118) of the respondents; (2) a group with average symptom scores slightly above the clinical
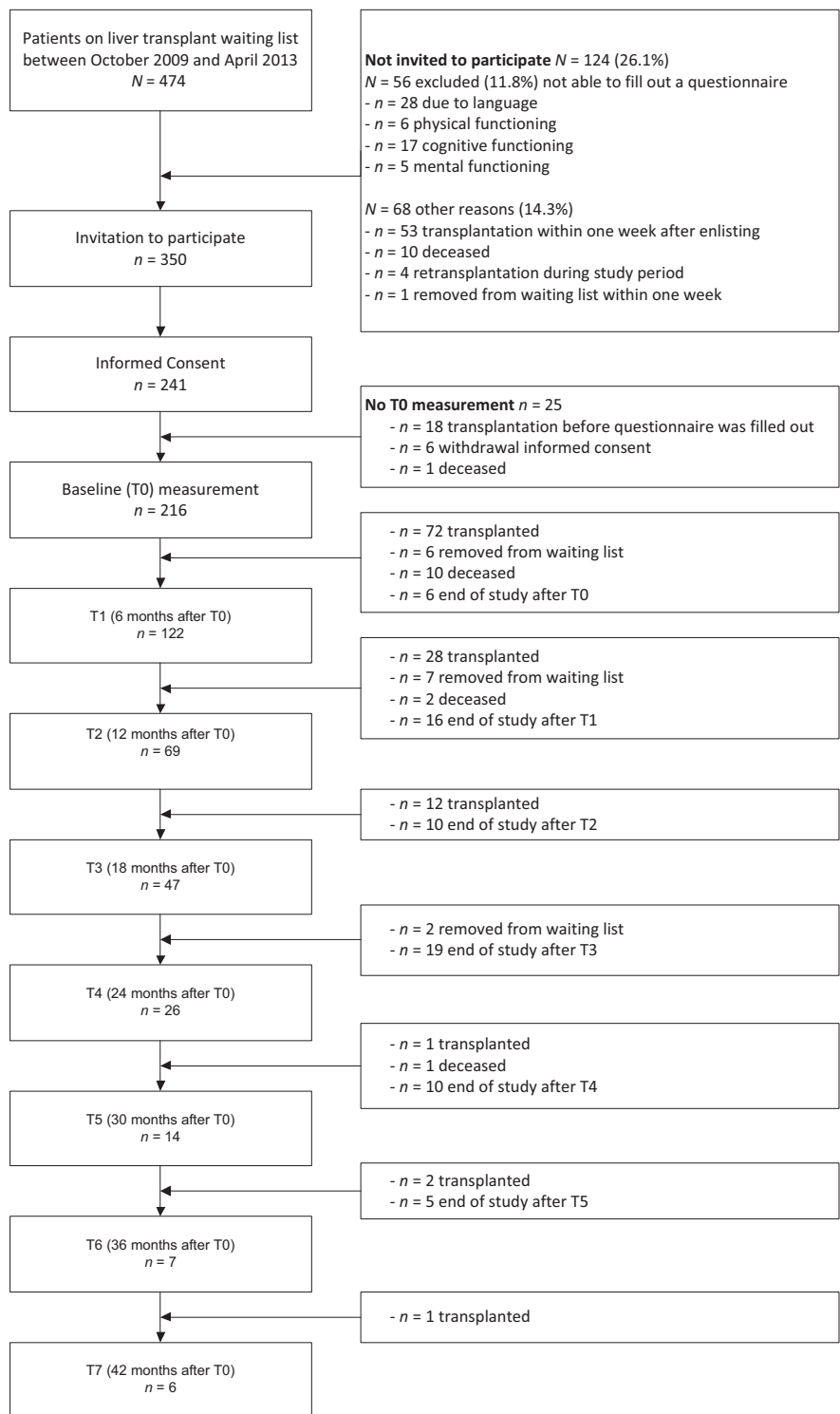
Figure 1. Study inclusion flow diagram.

Table 1. Baseline demographic, clinical, and individual characteristics of the study population

| Characteristic	All N = 216
N (%)	
Gender: male	144 (66.7)
Marital status: with partner	168 (87.8)
Educational level	
Low	47 (21.8)
Moderate	96 (44.4)
High	73 (33.8)
Employment status: paid job	64 (29.6)
Nationality: Dutch	200 (92.6)
Primary disease	
Biliary cirrhosis	78 (36.1)
Alcoholic cirrhosis	51 (23.6)
Metabolic disorder	24 (11.1)
Viral hepatitis	28 (13.0)
Cirrhosis of unknown origin	18 (8.3)
Miscellaneous	17 (7.8)
Hepato Cellular carcinoma	34 (15.7)
Mean (*SD*)	
Age (in years)	51.6 (11.3)
Number of comorbidities	1.9 (1.6)
Time since diagnosis (in years)	5.8 (6.3)
Time on waiting list (in months)	7.8 (13.9)
MELD score	13.3 (5.3)
LDSI score	9.5 (5.4)
Personal control	23.9 (5.4)
Coping style	
Emotional coping	19.2 (6.5)
Task-oriented coping	25.1 (4.3)
Avoidance coping	17.1 (5.0)
Number of life events	1.6 (1.3)

level, comprising 33.5% ($n = 67$) of the respondents; and (3) a group with average symptom scores high above clinical level, comprising 15.2% ($n = 31$) of the respondents. Sensitivity analyses using data of T0–T4 revealed three similar distinctive trajectories (BIC: 2 clusters: 1292.91; 3 clusters: 1288.92; 4 clusters: 1295.37), with an overlap in group membership in 94.4% of the cases. Regarding the stability of the trajectories over time, the effect sizes (η_p^2) were, respectively, .08 for trajectory 1, .15 for trajectory 2, and .20 for trajectory 3. This indicates that time accounted for 8–20% of the variability in anxiety scores within the trajectories.

Variables related with the trajectories of anxiety
As shown in Table 3, univariate ordinal logistic regression analyses revealed that the distinctive trajectories were independently related with the variables: educational level, the LDSI score, personal control, emotional coping, task-oriented coping, and the number of life events. Investigating the effects of these variables simultaneously on trajectory

Table 2. Parameters used for model selection regarding trajectories of symptoms of anxiety and depression

				%				
Model	BIC	AIC	Posterior probabilities	1	2	3	4	5
Symptoms of anxiety								
2	1355.64	1338.77	0.89–0.93	62.6	37.4	–	–	–
3	1349.24	1323.93	0.77–0.87	51.3	33.5	15.2	–	–
4	1354.92	1321.16	0.69–0.86	49.1	6.8	29.2	14.9	–
Symptoms of depression								
2	1860.24	1843.36	0.89–0.94	71.1	28.9	–	–	–
3	1835.48	1810.17	0.84–0.91	75.5	35.0	7.6	–	–
4	1824.75	1791.00	0.77–0.92	22.7	43.9	27.7	5.7	–
5	1833.85	1791.66	0.64–0.91	21.0	35.9	12.0	26.0	5.1
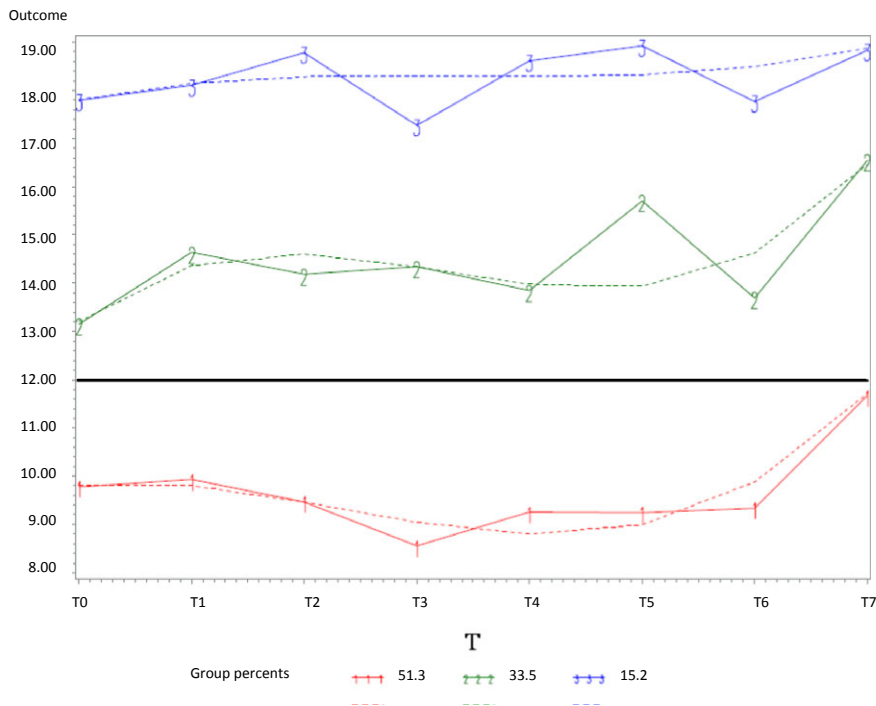
Figure 2. Distinct trajectories of symptoms of anxiety of liver transplant candidates during the waiting list period. *Note.* The bold black line represents the cut-off value (≥12) of the clinical level of symptoms of anxiety. T0 = baseline measurement, T1 = 6 months after T0, T2 = 12 months after T0, T3 = 18 months after T0, T4 = 24 months after, T5 = 30 months after T0, T6 = 36 months after T0, T7 = 42 months after T0. [Colour figure can be viewed at wileyonlinelibrary.com]

membership, using multiple ordinal logistic regression analysis, showed that educational level and the number of life events do not seem to help classify subjects when LDSI, personal control, emotional coping, and task-oriented coping are already provided

Table 3. Demographic, clinical, and individual characteristics of respondents within the distinct trajectories of anxiety

	Trajectory 1 Anxiety below clinical level *n* = 118	Trajectory 2 Anxiety slightly above clinical level *n* = 67	Trajectory 3 Anxiety high above clinical level *n* = 31	*p*-Value
n/%				
Gender: Male	78 (66.1)	46 (68.7)	20 (64.5)	.94
Marital status: Partner	91 (77.1)	53 (79.1)	24 (77.4)	.85
Educational level				
Low	23 (19.5)	11 (16.4)	13 (41.9)	.30
Moderate	57 (48.3)	31 (46.3)	8 (25.8)	**.04**
High	38 (32.2)	25 (37.3)	10 (32.3)	Ref.
Currently employed: Paid job	38 (32.2)	22 (32.8)	4 (12.9)	.17
Primary disease				
Biliary cirrhosis	45 (38.1)	25 (37.3)	8 (25.8)	.48
Alcoholic cirrhosis	29 (24.6)	16 (23.9)	6 (19.4)	.63
Metabolic disorder	11 (9.3)	8 (11.9)	5 (16.1)	.48
Viral hepatitis	14 (11.9)	6 (9.0)	8 (25.8)	.21
Cirrhosis of unknown origin	8 (6.8)	6 (9.0)	4 (12.9)	.29
Miscellaneous	11 (9.3)	6 (9.0)	–	.25
Hepato Cellular Carcinoma	21 (17.8)	10 (14.5)	3 (9.7)	.30
Mean (*SD*)				
Age	51.9 (11.3)	51.1 (11.7)	51.8 (11.0)	.79
Number of comorbidities	1.7 (1.4)	2.2 (1.9)	2.2 (1.5)	.06
Time since diagnosis (in years)	6.4 (7.0)	5.0 (4.8)	5.2 (5.8)	.12
Time on waiting list (in months)	6.9 (13.1)	7.9 (15.0)	9.5 (14.6)	.36
MELD score	13.3 (5.5)	12.9 (5.4)	14.5 (4.5)	.59
LDSI score	7.7 (4.9)	10.5 (4.3)	14.0 (5.7)	**<.001**
Personal control	26.1 (4.8)	22.3 (5.0)	19.1 (4.4)	**<.001**
Coping style				
Emotional coping	16.8 (5.4)	21.3 (6.8)	23.5 (5.9)	**<.001**
Task-oriented coping	25.9 (4.2)	25.0 (4.0)	22.6 (4.3)	**<.001**
Avoidance coping	16.6 (5.4)	17.6 (4.7)	17.4 (3.8)	.22
Number of life events	1.4 (1.1)	1.7 (1.4)	2.1 (1.5)	.01

Note. MELD = Model for End-stage Liver Disease; LDSI = Liver disease Symptom Index; ref. = reference category.
Bold values are significant.

(Table 4). The results of the OLR analysis showed that a unit increase in LDSI score (OR = 1.16, CI 1.09–1.23) and a unit increase in emotional coping score (OR = 1.13, CI 1.07–1.19) were related with an increase in the odds of membership in the trajectories with higher levels of anxiety, while a unit increase in personal control score (OR = 0.89, CI 0.84–0.95) and a unit increase in the task-oriented coping score (OR = 0.89, CI 0.82–0.96) reduced the odds of membership in trajectories with higher levels of symptoms of anxiety.

Trajectories of depression during the waiting-list period

Regarding depressive symptoms, the model with four distinct trajectories was found to be the best model, with the lowest BIC score, posterior probabilities >0.7, and the smallest

group still comprised >5% of the study population (Table 2). In Figure 3, the trajectory analyses of symptoms of depression are depicted. The four distinctive trajectories of depression identified can be characterized as follows: (1) a group with average symptom scores for depression below the clinical level, comprising 22.7% ($n = 36$) of the respondents; (2) a group with average symptom scores for depression slightly below clinical level, comprising 43.9% ($n = 104$) of the respondents; (3) a group with average symptom scores for depression slightly above clinical level, comprising 27.7% ($n = 66$) of the respondents; and (4) a group with average symptom scores for depression high above the clinical level, comprising 5.7% ($n = 10$) of the respondents. Sensitivity analyses, using data from T0–T4, revealed four similar distinctive trajectories (three clusters: 1746.55; four clusters: 1740.71; five clusters: 1750.09), with an overlap in group membership in 89.4% of the cases. Regarding the stability of the trajectories over time, the effect sizes (η_p^2) were, respectively, .07 for trajectory 1, .04 for trajectory 2, .03 for trajectory 3, and .20 for trajectory 4. This indicates that time accounted for 3% to 20% of the variability in depression scores within the trajectories.

Variables related with the trajectories of depression
As shown in Table 5, univariate OLR revealed that the trajectories of depression were independently related with the variables: employment status, presence of hepatocellular carcinoma, number of comorbidities, MELD score, the LDSI score, personal control, emotional coping, and task-oriented coping. Investigating the effects of these variables simultaneously on trajectory membership, with multiple OLR analyses, showed that employment status, the presence of hepatocellular carcinoma, the number of comorbidities, and the MELD score do not seem to help classify subjects, when LDSI, personal control, emotional coping, and task-oriented coping are already provided (Table 6). The results of the OLR analysis showed that a unit increase in the LDSI score (OR = 1.23, CI 1.15–1.32) and a unit increase in the emotional coping score (OR = 1.13, CI 1.07–1.18) were related with an increase in the odds of membership in trajectories with higher levels

Table 4. Unstandardized estimates, odds ratios, and 95% confidence intervals of characteristics related with the distinct trajectories of anxiety

Variable	Estimate	*p*-Value	Odds ratio	95% Confidence Interval Lower	Upper
Low educational level	0.14	.73	1.15	0.51	2.64
Middle educational level	−0.68	.09	0.51	0.23	1.11
High educational level	Reference				
LDSI score	0.14	**<.01**	1.16	1.09	1.23
Personal control	−0.11	**<.01**	0.89	0.84	0.95
Emotional coping style	0.12	**<.01**	1.13	1.07	1.19
Task-oriented coping style	−0.12	**<.01**	0.89	0.82	0.96
Number of life events	0.19	.11	1.21	0.96	1.53

Notes. LDSI = Liver Disease Symptom Index.
pseudo-R^2 = 0.40 (Cox & Snell), 0.47 (Nagelkerke); Model χ^2 (423) = 403.27, p = .75.
Bold values are significant.
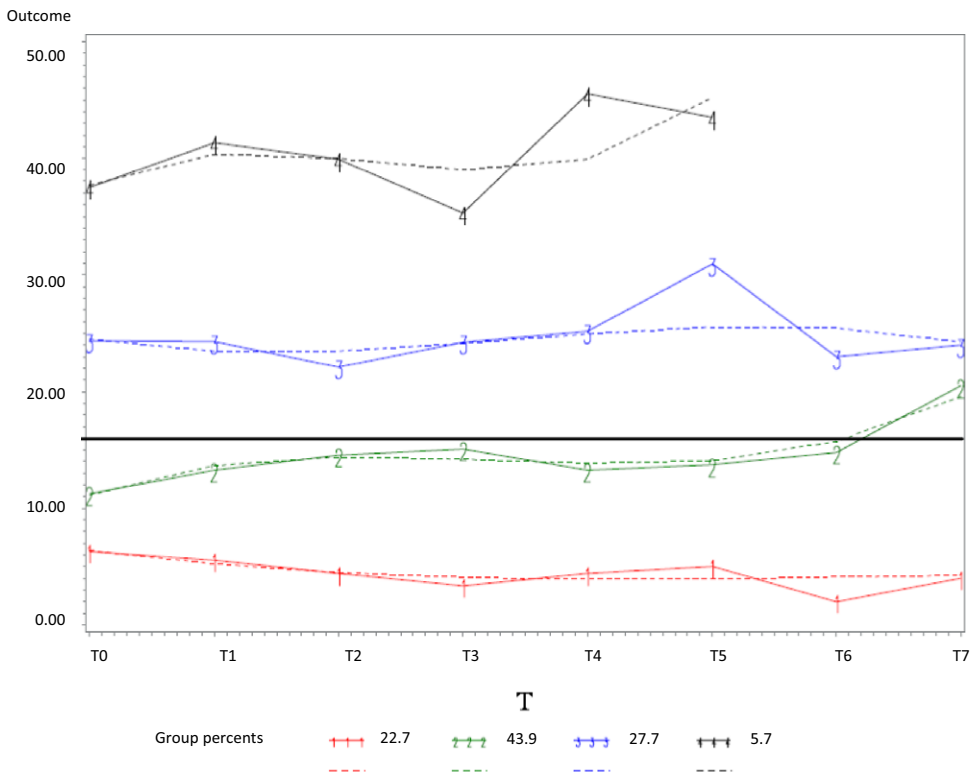
Figure 3. Distinct trajectories of symptoms of depression of liver transplant candidates during the waiting-list period. *Note.* The bold black line represents the cut-off value (≥16) of the clinical level of symptoms of depression. T0 = baseline measurement, T1 = 6 months after T0, T2 = 12 months after T0, T3 = 18 months after T0, T4 = 24 months after, T5 = 30 months after T0, T6 = 36 months after T0, T7 = 42 months after T0. [Colour figure can be viewed at wileyonlinelibrary.com]

of depression, whereas a unit increase in the personal control score (OR = 0.84, CI 0.78–0.90) and a unit increase in the task-oriented coping score (OR = 0.91, CI 0.85–0.98) were related with a decrease in the odds of membership in the trajectories with higher levels of depressive symptoms.

Discussion

This study showed that distinct trajectories of anxiety and depression are present in liver transplant candidates. Regarding symptoms of anxiety, three distinct trajectories were identified as follows: 1) below clinical level, 2) slightly above clinical level, and 3) high above clinical level, comprising, respectively, 51%, 34%, and 15% of the respondents. With respect to depressive symptoms, four distinct trajectories were identified as follows: (1) below clinical level, (2) slightly below clinical level, (3) slightly above clinical level, and (4) high above clinical level, comprising, respectively, 23%, 34%, 28%, and 6% of the respondents. All trajectories were stable over time. Time accounted for 8–20% of the variance in scores within the trajectories of anxiety and for 3–20% in the variance of scores in the trajectories of depression. The stability of the trajectories over time seems to

Table 5. Demographic, clinical, and individual characteristics of respondents within the distinct trajectories of depression

	Trajectory 1 Depression below clinical level n = 36	Trajectory 2 Depression slightly below clinical level n = 104	Trajectory 3 Depression slightly above clinical level n = 66	Trajectory 4 Depression high above clinical level n = 10	p-Value
n (%)					
Gender: Male	21 (58.3)	71 (68.3)	45 (68.2)	7 (70.0)	.40
Marital status: Partner	28 (77.8)	81 (77.9)	52 (78.8)	7 (70.0)	.91
Educational level					
Low	9 (25.0)	17 (16.3)	16 (24.2)	5 (50.0)	.45
Moderate	16 (44.4)	52 (50.0)	24 (36.4)	4 (40.0)	.25
High	11 (30.6)	35 (33.7)	26 (39.4)	1 (10.0)	Ref.
Employment status: Paid job	16 (44.4)	35 (33.7)	13 (19.7)	0 (0)	**.001**
Primary disease					
Biliary cirrhosis	15 (41.7)	37 (35.6)	24 (36.4)	2 (20.0)	.53
Alcoholic cirrhosis	9 (25.0)	23 (22.1)	16 (24.2)	3 (30.0)	.82
Metabolic disorder	5 (13.9)	10 (9.6)	5 (7.6)	4 (40.0)	.92
Viral hepatitis	3 (8.3)	14 (13.5)	10 (15.7)	1 (10.0)	.49
Cirrhosis of unknown origin	1 (2.8)	10 (9.6)	7 (10.6)	0 (0)	.52
Miscellaneous	3 (8.3)	10 (9.6)	4 (6.1)	0 (0)	.38
Hepato Cellular Carcinoma	9 (25.0)	20 (19.2)	4 (6.1)	1 (10.0)	**.01**
Mean (SD)					
Age (in years)	50.6 (11.2)	52.2 (12.0)	50.9 (11.1)	54.2 (5.7)	.89
Number of comorbidities	1.4 (1.1)	1.9 (1.6)	1.9 (1.7)	3.6 (1.6)	**.01**
Time since diagnosis (in years)	6.0 (6.0)	6.2 (6.7)	5.3 (5.7)	4.1 (6.5)	.32
Time on waiting list (in months)	9.4 (16.2)	5.7 (11.7)	9.5 (16.1)	8.4 (7.3)	.53
MELD score	11.1 (4.9)	13.5 (5.6)	14.3 (4.9)	13.7 (5.4)	**.01**
LDSI score	4.8 (3.9)	8.5 (4.2)	13.0 (5.3)	13.1 (4.0)	**<.01**
Personal control	28.1 (4.2)	25.1 (4.5)	20.9 (4.6)	15.5 (4.7)	**<.01**
Coping style					
Emotional coping	16.3 (4.8)	17.5 (5.5)	22.3 (6.4)	27.4 (7.2)	**<.01**
Task-oriented coping	26.8 (3.9)	25.4 (4.2)	24.3 (4.3)	21.9 (4.6)	**<.01**
Avoidance coping	17.5 (5.6)	17.0 (5.1)	17.1 (4.6)	15.7 (5.0)	.55
Number of life events	1.3 (1.1)	1.5 (1.2)	1.8 (1.4)	1.5 (1.4)	.09

Note. MELD = Model for End-stage Liver Disease; LDSI = Liver Disease Symptom Index; ref. = reference category.
Bold values are significant.

indicate that the baseline measurement is indicative of the level of depression and anxiety of liver transplant candidates during the waiting-list period.

These results confirmed two of our hypotheses, namely that the majority of transplant candidates would show low symptom levels of anxiety and depression and that a small subset would show high symptom levels. These findings are in line with studies analysing trajectories in other patient groups (Henselmans *et al.*, 2010; Lam *et al.*, 2013; Ng *et al.*, 2015; Yohannes *et al.*, 2016). However, in contrast to other studies, our third hypothesis, that a subset of the transplant candidates would show an increase in symptom level, was

Table 6. Unstandardized estimates, odds ratios, and 95% confidence intervals of characteristics related with the distinct trajectories of depression

Variable	Estimate	p-Value	Odds Ratio	95% Confidence Interval	
				Lower	Upper
Employment (if yes)	−0.31	.36	0.73	0.38	1.42
Hepatocellular carcinoma (if yes)	−0.24	.58	0.79	0.35	1.80
Number of comorbidities	0.02	.87	1.02	0.84	1.22
MELD score	0.03	.34	1.02	0.97	1.08
LDSI score	0.22	**.00**	1.23	1.15	1.32
Personal control	−0.18	**.00**	0.84	0.78	0.90
Emotional coping style	0.12	**.00**	1.13	1.07	1.18
Task-oriented coping style	−0.09	**.01**	0.91	0.85	0.98

Notes. MELD = Model for End-stage Liver Disease; LDSI = Liver Disease Symptom Index.
pseudo- R^2 = 0.53 (Cox & Snell), 0.58 (Nagelkerke); Model χ^2 (639) = 424.44, p = 1.000.
Bold values are significant.

not confirmed. Instead, we found that a substantial part of the transplant candidates showed stable symptom levels slightly above the clinically relevant level of anxiety and depression. This might be related to the ongoing feelings of uncertainty during the waiting period for a donor organ.

Of all the demographic, clinical, and individual characteristics examined, four variables were found to be independently related with both the trajectories of anxiety and depression: the LDSI score, personal control, and emotional and task-oriented coping. In contrast to studies that have analysed associations at a group level (Corruble *et al.*, 2011; Lopez-Navas *et al.*, 2011; Sainz-Barriga *et al.*, 2005; Santos *et al.*, 2010), we found no relations between demographic characteristics, such as age, sex, marital status, and employment status and the trajectories of either anxiety or depression. However, these finding are in line with other studies examining variables related with trajectories of anxiety and depression in other patient groups, in which also clinical and individual variables, such as physical symptoms and coping strategies, were found to be predictive of trajectories of psychological distress and no relations were found with demographic variables (Bonanno, Kennedy, Galatzer-Levy, Lude, & Elfström, 2012; Henselmans *et al.*, 2010; Lam *et al.*, 2013; Van den Broek *et al.*, 2014).

Regarding clinical characteristics, only the LDSI score, the severity of liver disease symptoms as perceived by the transplant candidate, was found to be related with the trajectories of anxiety and depression. Respondents who perceived the liver disease symptoms as more severe had a higher probability of being in the trajectories with higher levels of anxiety and depression. This finding emphasizes that adequate management of liver disease symptoms is necessary. However, the LDSI is a subjective measurement of disease severity, and this finding was not supported by an objective measurement of disease severity, such as the MELD score. This may imply that altering the cognitive appraisal of disease symptoms by giving adequate procedural and sensory information about liver disease symptoms and possible self-management strategies may help transplant candidates to cope with their deteriorating health. However, it is acknowledged that some liver disease symptoms (e.g., itch and fatigue) are hard to treat. Therefore, this aspect needs to be examined in future research.

The individual characteristics of personal control and coping seem to play a major role in the development and maintenance of symptoms of anxiety and depression. Transplant candidates with a lower level of personal control, who feel that they have no control over the things that happen to them, and those who make more use of emotional coping, were more likely to be in the trajectories with high symptom levels of both anxiety and depression. Transplant candidates with a high level of personal control and who make more use of task-oriented coping, on the other hand, seem to be less anxious and depressed. Therefore, interventions aimed at empowering transplant candidates by strengthening coping skills or sense of control may help to reduce symptoms of anxiety and depression during the waiting-list period. However, evidence regarding effective psychosocial interventions in transplant candidates is lacking (Cupples *et al.*, 2006; Engle, 2001). So far, only a few studies, reporting (preliminary) findings regarding psychosocial interventions in transplant candidates and recipients, showed that this may be effective in reducing distress (Dew *et al.*, 2004; Hsiao *et al.*, 2016; Napolitano *et al.*, 2002; Reilly-Spong, Reibel, Pearson, Koppa, & Gross, 2015). In future studies, the effectiveness of psychosocial interventions to address psychological problems in transplant candidates needs to be examined.

The clinical implication of our study is that identifying transplant candidates at risk of psychological distress is warranted early in the transplant process by the use of routine screening of psychological problems as well as variables of influence on the psychological functioning of transplant candidates. Although the importance of screening for psychological problems has been widely recognized (Olbrisch, Benedict, Ashe, & Levenson, 2002), common practice may vary between transplant centres, and psychosocial screening is a less standardized procedure (Maldonado *et al.*, 2012). In the literature, several instruments to perform a structured psychosocial assessment of transplant candidates have been described, of which the 'Stanford Integrated Psychosocial Assessment for Transplantation' (SIPAT) (Maldonado *et al.*, 2012) seems the most promising. The SIPAT assesses psychological functioning as well as risk factors, such as coping style and individual traits, of influence on adverse outcomes after transplantation. Based on the psychosocial screening, interventions tailored to the patient's needs, such as supportive counselling, mindfulness based stress reduction, or coping skills training, can be undertaken to enhance the psychological well-being of transplant candidates. In addition to psychosocial interventions aimed at reducing distress, referral for psychological or psychiatric counselling may contribute to better psychological well-being during the waiting-list period, which ultimately may in turn contribute to better outcomes after transplantation.

The strength of our study was its prospective, longitudinal, and multicentre design which made it possible to study the evolution of psychological problems over time. The overall sample size ($n = 216$) was reasonable, and the response rate of 69% was satisfactory. Furthermore, a full range of related variables (demographic, clinical, and individual) was examined. However, the sample size was relatively small for trajectory analysis. In addition, the use of a dynamic cohort led, resulting in non-random subject dropout, could have influenced the results of our study. The generalizability of our results may, therefore, be limited, and replication of our findings in larger sample sizes is warranted.

In conclusion, distinct trajectories of symptoms of anxiety and depression were present in liver transplant candidates. The trajectories with symptom levels above clinical relevant levels for anxiety or depression comprised, respectively, 49% and 34% of the respondents. The stability of these trajectories over time seems to indicate that the baseline measurement is indicative of the course of symptoms of anxiety and depression

during the waiting-list period. Experiencing more liver disease symptoms, a lower level of personal control, making more use of emotional coping, and making less use of task-oriented coping increased the odds of membership in trajectories with higher symptom levels for both the trajectories of anxiety and of depression. Therefore, screening of psychological problems and related risk factors early in the transplant process – if not already established – is recommended. Subsequently, appropriate interventions aimed at reducing distress should be undertaken to optimize the psychological well-being of the transplant candidate. However, evidence regarding the effectiveness of psychosocial interventions in organ transplant candidates is lacking and needs to be studied in future research.

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Conflict of interest

All authors declare no conflict of interest.

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