**Running title: Cognitions, emotions, and diabetes self-care**

**What are the combined effects of negative emotions and illness cognitions on self-care in people with type 2 diabetes? A longitudinal structural equation model**

**Joanna L Hudson\*1,2, PhD, Christine Bundy2, PhD, Peter Coventry2, PhD, Chris Dickens3, PhD, Alex Wood, PhD4,5, PhD, and David Reeves6,7, PhD,**

1 Health Psychology Section, Psychology Department, Institute of Psychiatry, Psychology, And Neuroscience, King’s College London, UK (Present address)

2 NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) – Greater Manchester and Manchester Academic Health Science Centre, University of Manchester, UK.

**3**Mental Health Research Group, Institute of Health Research, University of Exeter Medical School and the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for the South West Peninsula (PenCLAHRC), UK

4Behavioral Science Centre, Stirling Management School, University of Stirling, 3Y8 Cottrell Building, Stirling Management School, University of Stirling, Stirling, Scotland, FK9 4LA

**5**Manchester Centre for Health Psychology, School of Psychological Sciences, University of Manchester, UK

6NIHR School for Primary Care Research, Centre for Primary Care, University of Manchester, Manchester, UK

7Centre for Biostatistics, University of Manchester, Manchester, UK

WORD COUNT: 7394

**Corresponding author:**

Joanna L Hudson

Health Psychology Section

Psychology Department
Institute of Psychiatry, Psychology and Neuroscience
King's College London
5th floor Bermondsey Wing

Guy's Campus
London Bridge
London
SE1 9RT

Email: Joanna.Hudson@kcl.ac.uk; Tel: +77 0207 188 1189

Christine Bundy1.530 Stopford Building
University of Manchester
Oxford Road
Manchester
M13 9PT

christine.bundy@manchester.ac.uk

Tel: +44 (0)161 275 5231

Peter Coventry

Centre for Primary Care: Institute of Population Health
University of Manchester
Room 6.02, Williamson Building
Oxford Road
Manchester
M13 9PL

Peter.A.Coventry@manchester.ac.uk

Chris Dickens

College House

University of Exeter Medical School

St Luke’s Campus

United Kingdom

EX1 2LU

UK

C.M.Dickens@exeter.ac.uk

Alex Wood

3B54 Cottrell Building

Stirling Management School

University of Stirling

Stirling

Scotland

FK9 4LA

alex.wood@stir.ac.uk.

David Reeves

Centre for Primary Care
Institute for Population Health
University of Manchester
Williamson Building
Oxford Road
Manchester
M13 9PL

david.reeves@manchester.ac.uk

**What are the combined effects of negative emotions and illness cognitions on self-care in people with Type 2 diabetes? A longitudinal structural equation model**

**Abstract**

***Objective*** To explore whether negative emotions mediate the effect of diabetes cognitions on diabetes self-care and conversely whether diabetes cognitions mediate the effect of negative emotions on diabetes self-care.

***Design*** Longitudinal observational study in adults with Type 2 diabetes.

***Main outcome measures*** Self-reported depression and anxiety (Diabetes Wellbeing Questionnaire), cognitions (Illness Perceptions Questionnaire-Revised; Beliefs about Medicines Questionnaire), and diabetes self-care (Summary of Diabetes Self-Care Activities Scale) were completed at baseline and six months. Analyses used structural equation modelling.

***Results*** Baseline medication concerns were associated with elevated symptoms of depression and anxiety at follow-up, but emotions did not mediate medication concern’s effect on diabetes self-care. Baseline depression and anxiety symptoms were associated with specific diabetes cognitions over time, but these cognition domains did not mediate emotion’s effect on diabetes self-care. Personal control remained independent of emotions and was associated with diabetes self-care over time.

***Conclusions*** Negative emotions did not act directly or alongside cognitions to influence diabetes self-care. The reciprocal relationship between diabetes cognitions and emotions suggests cognitive restructuring, in addition to other mood management intervention techniques would likely improve the emotional wellbeing of adults with Type 2 diabetes. Likewise, personal control beliefs are likely important intervention targets for improving self-care.

**Key words:**

 Depression, anxiety, illness cognitions, diabetes self-care, structural equation modelling**,** longitudinal

# Introduction

In adults with diabetes, symptoms of depression and anxiety are prevalent ([Anderson, Freedland, Clouse, & Lustman, 2001](#_ENREF_1); [Grigsby, Anderson, Freedland, Clouse, & Lustman, 2002](#_ENREF_16)) and associated with increased glycosylated haemoglobin (HbA1c) ([Lustman et al., 2000](#_ENREF_30)), morbidity ([de Groot, Anderson, Freedland, Clouse, & Lustman, 2001](#_ENREF_12)), and mortality ([Park, Katon, & Wolf, 2013](#_ENREF_35)). Both biological ([Rustad, Musselman, & Nemeroff, 2011](#_ENREF_40)) and behavioural ([Gonzalez et al., 2008](#_ENREF_15)) mechanisms influence relationships between symptoms of depression and anxiety and poorer diabetes health outcomes. However, a detailed understanding of the behavioural mechanisms responsible for the relationship between depression and anxiety and poorer diabetes health outcomes is lacking.

 A behavioural theory used to understand what motivates self-care behaviour in the context of illness is the Common Sense Self-Regulation Model (CS-SRM) ([Leventhal, Meyer, & Nerenz, 1980](#_ENREF_28)). The CS-SRM argues that when presented with a health threat we initiate parallel cognitive and emotional responses. Indeed the CS-SRM hypothesises that reciprocal causal relationships exist between illness cognitions and emotional responses, which then go on to determine the types of illness self-care and emotional coping behaviours implemented by an individual. Thus it provides an appropriate framework to explore how depression and anxiety operates in the context of chronic illness.

The cognitive response of the CS-SRM includes an appraisal of the health threat to generate an illness representation framework. This includes illness cognitions about the perceived cause of the health threat, associated symptoms, and their likely duration and predictability. It also includes cognitions about the degree of personal and treatment resources available for health threat management, its impact on functioning, and the extent to which a person has a coherent understanding of the health threat. A person’s illness representation framework determines the types of self-care behaviours a person might implement to manage the health threat.

Specifically in the context of diabetes, cross-sectional observational studies have confirmed the importance of the relationship between illness cognitions and diabetes self-care. Having an optimistic diabetes appraisal including perceiving diabetes treatments to be effective and believing that one has personal resources available for managing diabetes demonstrates relatively consistent associations with improved adherence to one or more diabetes self-care behaviours: diet, exercise, and medication taking ([Broadbent, Donkin, & Stroh, 2011](#_ENREF_9); [Hampson, Glasgow, & Foster, 1995](#_ENREF_18); [Hampson, Glasgow, & Toobert, 1990](#_ENREF_19); [Searle, Norman, Thompson, & Vedhara, 2007](#_ENREF_41)). Conversely, having a pessimistic appraisal of diabetes including perceiving diabetes to cause a high number of physical and social consequences ([Barnes, Moss-Morris, & Kaufusi, 2004](#_ENREF_3); [Broadbent et al., 2011](#_ENREF_9); [Hampson et al., 1990](#_ENREF_19)) in addition to perceiving diabetes as an unpredictable condition ([Barnes et al., 2004](#_ENREF_3)) is associated with lower adherence to diabetes self-care behaviours.

The CS-SRM acknowledges with equal emphasis the role of the emotional response to the health threat. This includes an emotional reaction (e.g. depression and anxiety), thus coping behaviours are simultaneously initiated to manage these emotions, for example, avoidance of medical settings. The relationship between diabetes emotional responses and coping behaviours (e.g. avoidance, withdrawal, denial) to our knowledge has not been directly assessed, but indirectly inferred from studies demonstrating lower rates of adherence among people with higher levels of depression ([Gonzalez et al., 2008](#_ENREF_15)).

Empirical studies based on the CS-SRM have largely used cross-sectional designs and focussed on investigating direct pathways leading from illness cognitions to diabetes self-care behaviours. These studies have not taken into account the hypothesised reciprocal relationships that occur between illness cognitions and emotional responses and their subsequent combined effects on diabetes self-management. Thus studies have only tested partial aspects of the CS-SRM. In the context of diabetes, cross-sectional evidence across nine studies indicates that having a pessimistic cognitive appraisal of diabetes heightens a person’s experience of negative emotions or vice versa ([Hudson, Bundy, Coventry, & Dickens, 2014](#_ENREF_22)). However, we are aware of no longitudinal studies which have explored simultaneously the direct and indirect pathways through which illness cognitions and emotional responses operate to have downstream effects on diabetes self-care.

 Our study thus tested the salience of the CS-SRM. We longitudinally explored using structural equation modelling (SEM) both direct and indirect (mediated) relationships between diabetes cognitions, negative emotions, and diabetes self-care behaviours. We used SEM to explore if: i) cognitions can have a direct effect on diabetes self-care and also an indirect effect mediated through negative emotions; ii) negative emotions can have a direct effect on diabetes self-care and also an indirect effect mediated through cognitions. The hypothesised nature and direction of effects between variables is detailed below. It was not possible to define a priori the specific cognition-emotion pathways that would demonstrate a relationship with diabetes self-care because no prior studies have examined simultaneously these multiple mediator pathways over time in adults with type 2 diabetes.

***Study hypotheses***

1. Having a pessimistic cognitive appraisal of diabetes will be directly associated with lower adherence to diabetes self-care (cognitions →diabetes self-care).
2. Having a pessimistic cognitive appraisal of diabetes will be indirectly associated with lower adherence to diabetes self-care via heightened negative emotions (cognitions → emotions → diabetes self-care)
3. Heightened negative emotions will be directly associated with lower adherence to diabetes self-care (emotions → diabetes self-care)
4. Heightened negative emotions will be indirectly associated with lower adherence to diabetes self-care via pessimistic cognitive appraisals of diabetes (emotions → cognitions → diabetes self-care)

# Materials and Method

## *Participants*

 At baseline people with Type 2 diabetes were recruited consecutively (face to face) from a UK diabetes outpatient clinic (central Manchester) from May 2011 to October 2011 (ethical approval reference 11/NW/0069). Participants were followed up at six months to coincide with their next bi-annual review at the outpatient clinic. Outpatients were eligible for inclusion if they had diagnosed Type 2 diabetes and were ≥ 18 years old, but were ineligible if they had an impairment that was deemed inappropriate for participation by the person themselves, a carer or their medical team (e.g. lacked capacity, high risk of suicide).

## *Measures*

 The following data were collected at baseline and six months follow-up after informed consent:

### *Demographic and Clinical Characteristics (baseline only)*

Self-reported demographics: age, gender, and ethnicity. Clinical characteristics were extracted from medical records: diabetes duration, diabetes medication type, number of diabetes complications (retinopathy, neuropathy, nephropathy, cardio-vascular, cerebrovascular, peripheral vascular, and metabolic), and number of other health co-morbidities (according to International Classification of Diseases categories ICD-10) ([World Health Organization, 2010](#_ENREF_46)).

### *Depression and Anxiety*

Depressive and anxious symptoms were measured using the Diabetes Wellbeing Questionnaire (DWBQ) ([Bradley, 1994](#_ENREF_8)). The DWBQ has four subscales: depression (six items), anxiety (six items), energy (four items), and positive wellbeing (six items). DWBQ items are responded to on a four point Likert scale. Only the depression and anxiety subscales were used. These subscales were adapted from Zung’s self-rating depression ([Zung, Richards, & Short, 1965](#_ENREF_48)) and anxiety ([Zung, 1974](#_ENREF_47)) scales specifically for use among the diabetes population. The DWBQ depression and anxiety subscales demonstrate high concurrent validity with the Hospital Anxiety and Depression scale ([Pincus, Griffiths, Isenberg, & Pearce, 1997](#_ENREF_38)). Higher DWBQ scores indicate higher depressive and anxious symptoms.

### *Diabetes Illness Cognitions*

Illness cognitions were measured using the revised Illness Perception Questionnaire (IPQ-R) ([Moss-Morris et al., 2002](#_ENREF_34)) and the Beliefs about Medicines Questionnaire-specific (BMQ-specific) ([Horne, Weinman, & Hankins, 1999](#_ENREF_21)). The IPQ-R assesses the following illness cognition domains (subjective beliefs; 70 items): identity (symptoms attributed to diabetes), timeline acute/chronic (diabetes duration), timeline cyclical (predictability of diabetes), cause (cause of diabetes), consequences (impact of diabetes), personal control (availability of individual resources for managing diabetes), treatment control (efficacy of treatments for managing diabetes), illness coherence (degree of diabetes understanding), and emotional representations (negative emotions experienced because of diabetes). All IPQ-R items use a five point Likert scale excluding identity, which has a binary yes/no response based on whether symptoms are experienced and attributed to diabetes. All yes responses receive a score of one and are summed. High scores on each subscale indicate stronger endorsements of the construct measured. The BMQ-specific ([Horne et al., 1999](#_ENREF_21)) has two subscales: medication concerns (perceived negative effects of taking medications; 5 items) and medication necessity (perceived need for taking medication to manage diabetes; 5 items). Both subscales contain five point Likert response items; higher scores indicate a stronger degree of belief in the construct.

### *Diabetes Self-Care Behaviours*

The Summary of Diabetes Self-Care Activities Scale (SDSCA) ([Toobert, Hampson, & Glasgow, 2000](#_ENREF_42)) was used to measure diabetes self-care behaviours. Participants indicated the extent to which they adhered to the following behaviours over the last seven days (eight point Likert scale ranging from zero to seven days): i) general diet (following a healthy eating plan), ii) specific diet (fruit and vegetable and fat intake), iii) exercise, iv) self-monitoring of blood glucose (SMBG), v) foot care, and vi) medication adherence. Higher scores indicate greater adherence. We combined scores across the individual SDSCA items to generate a single overall outcome measure of diabetes self-care. The diabetes self-care outcome represents the mean number of days per week a person adhered to their multi-dimensional diabetes self-care routine, an approach used by others to determine overall levels of diabetes self-care ([Walker, Gebregziabher, Martin-Harris, & Egede, 2015](#_ENREF_44)).

## *Statistical Analysis*

 Data were non-normally distributed. Descriptive statistics are reported as means and standard deviations given our relatively large sample size. Mann-Whitney U tests and Pearson chi-square tests were used to compare demographic and clinical characteristics between completers and non-completers at follow-up. Bootstrapping (10,000 resamples) was applied to account for non-normally distributed outcomes ([Mooney & Duval, 1993](#_ENREF_33)).

## *Analytical model building*

We used a two-phase approach to building and testing our analytical models of the relationships between cognitions, emotions, and diabetes self-care. In Phase 1 we used traditional bivariate regression models to statistically test hypothesised direct and indirect pathways from cognitions and emotions to diabetes self-care; in Phase 2 we used SEM procedures, with measured variables only, to simultaneously evaluate the multiple pathways identified as statistically significant in Phase 1, to arrive at the final models. As well as testing the statistical significance of each individual pathway within the model, SEM also provides an overall assessment of how well hypothesised relationships reflect actual observed relationships in the sample dataset, providing an overall test of model validity ([Kline, 2005](#_ENREF_27)). Goodness of fit indices are used to evaluate the overall model (See Table 1) ([Kline, 2005](#_ENREF_27)).

[INSERT TABLE 1 HERE]

### *Phase 1 Bivariate Analyses*

Whilst the CS-SRM explicitly states that cognitions and emotions have the potential to directly and indirectly affect illness management behaviours, the specific pathways that apply longitudinally in the context of an outpatient Type 2 diabetes population are not known. We undertook initial (Phase 1) bivariate regression analyses in order to empirically identify potentially important direct and indirect relationships between cognitions, emotions, and diabetes self-care, for subsequent simultaneous testing using SEM. This step was necessary because simultaneous entry of all plausible directional pathways between the eight illness cognition domains, depression, anxiety, and diabetes self-care would have led to high multicollinearity due to inter-correlated cognition domains and an unacceptably low participant to parameter ratio, affecting the reliability of the path coefficients. The bivariate phase was therefore used to filter out non-existent or very weak paths as a first step. We therefore used a high alpha-level to avoid prematurely excluding potentially important pathways and a pathway was retained for use in SEM analyses if it was statistically significant in bivariate regression analyses at an alpha of ≤10%.

Bivariate regression models were constructed to evaluate the direct effects summarised below:

|  |  |  |
| --- | --- | --- |
| Baseline explanatory variables (Time 1) | Directional pathway | Outcome variables at follow-up (Time 2) |
| Cognitions  | → | Emotions |
| Emotions | → | Cognitions |
| Cognitions | → | Diabetes self-care |
| Emotions | → | Diabetes self-care |

Bivariate regression analyses also provided a test of indirect effects. Because we were limited to two time points of data collection, we applied a modified version of the Baron and Kenny ([1986](#_ENREF_4)) approach to test for the presence of indirect effects (mediation). We used Cole and Maxwell’s ([2003](#_ENREF_11)) two step procedure.

1. Step one: Identify if the baseline explanatory variable (time 1) has a directional effect on the hypothesised mediator at follow-up (time 2) (i.e. regress the mediator at time 2 on both the explanatory and mediator variable at baseline, time 1)
2. Step two: Identify if the baseline mediator variable (time 1) has a directional effect on the outcome variable at follow-up (time 2) (i.e. regress the outcome variable at time 2 on both the mediator and outcome variable at baseline, time 1).

This two-step approach allowed us to use our two waves of data collection so that: i) the effect of the explanatory variable on the mediator variable and ii) the effect of the mediator variable on the outcome variable were both tested using prospective analyses as opposed to limiting one aspect of our mediation pathway to a contemporaneous analysis only.

### *Phase 2 SEM Model specification*

We produced separate SEM models for depression and anxiety because of multicollinearity between these variables (r=0.71). In each model we initially included all pathways identified as (separately) statistically significant at an alpha of ≤10% in the Phase 1 bivariate regression analyses. Starting from this initial model, we sequentially trimmed pathways from the model, at each step removing the pathway with the highest p value, until all remaining pathways were significant at an alpha of ≤ 5%. This approach allows the generation of parsimonious models and promotes translation into clinical interventions ([Kline, 2005](#_ENREF_27)).

In a subsequent step we assessed the impact of potential confounders on the relationships in the final models. The impact of each potential confounder was explored separately to retain statistical power and reliability of the estimates (see phase 1 bivariate analyses for rationale). The confounders examined were: age, gender, ethnicity (white vs non-white), diabetes duration, number of diabetes complications, number of co-morbidities, and medication type (oral medication insulin/injection therapy). SEM was conducted using IBM SPSS version 19 ([IBM SPSS Statistics, 2010](#_ENREF_23)) and Analysis of Moment Structures (AMOS) ([Arbuckle, 2007](#_ENREF_2)) statistical software and used complete cases analyses.

# Results

 Figure 1 shows the flow of participants through the study. Of the 441 participants approached at baseline, 261 completed baseline questionnaires (59% response rate). Of these, 194 participants completed six month follow-up questionnaires (74% retention rate). A greater proportion of completers were of white ethnicity than non-completers (72.2% vs 43.1%, p≤0.001). No other differences were found. Table 2 summarises socio-demographic and clinical characteristics of the 194 participants who returned follow-up questionnaires. Table 3 summarises mean scores on self-report measures at six months follow-up.

INSERT FIG 1 AND TABLES 2 AND 3 HERE]

***Bivariate regression analyses***

Statistical appendix 1 (online supplement) presents regression coefficients and p values for all bivariate regression pathways tested. Pathways that showed a relationship with the outcome variable at alpha ≤10% are highlighted and were included for robust simultaneous testing using SEM. Figures 2 and 3 summarises the final depression and anxiety models. They include only those pathways that remained statistically significant using an alpha of 0.05 when evaluated simultaneously alongside other explanatory and outcome variables using SEM.

## *Structural Model of Relationships between Diabetes Cognitions, Negative Emotions, and Diabetes Self-Care*

### *SEM model: Diabetes Cognitions, Depression and Diabetes Self-Care*

The solid directional arrows in Figure 2 summarises the final SEM of the longitudinal relationships between cognitions, depression, and diabetes self-care. Only three pathways remained statistically significant when evaluated simultaneously. Participants who were more concerned about their diabetes at baseline were more likely to demonstrate higher depressive symptoms at six months; thus demonstrating a direct effect from cognitions (explanatory variable) to emotions (mediator). As such these findings met Cole and Maxwell’s (2003) step one criterion for the initial part of the cognition → emotion → diabetes self-care pathway. However, as indicated by an absent directional pathway from baseline depression to diabetes self-care at six months, the effect of the mediator (depression) on the outcome (diabetes self-care) was not supported. Conversely, participants with higher depression scores at baseline were more likely to believe that their diabetes was unpredictable (timeline cyclical) at six months follow-up. Thus demonstrating a direct effect from emotions (explanatory variable) to cognitions (mediator variable). This finding met Cole and Maxwell’s (2003) step one criteria for the emotion → cognition → diabetes self-care pathway. However, the pathway leading from baseline timeline cyclical (mediator variable) to diabetes self-care (outcome variable) at six months follow-up is absent from Figure 2. The effect of the mediator on the outcome was not supported according to Cole and Maxwell’s (2003) step two criteria. Baseline personal control beliefs acted autonomously from depression and had a direct effect on adherence to diabetes self-care at six months follow-up. Individuals who felt more confident in their ability to manage their diabetes at baseline showed reduced adherence to their diabetes treatment regimens over time.

 We evaluated the statistical fit of the model using the goodness of fit indices and criteria summarised in Table 1. The model shown in Figure 2 had evidence of good statistical fit on all model fit indices (χ²=36.47, dfm=27, p=0.11; RMSEA=.05, CFI=.98, SRMR=.05, N=154).

[INSERT FIGURE 2 HERE]

### *SEM model: Diabetes cognitions, Anxiety, and Diabetes Self-Care*

 The solid arrows in Figure 3 depicts the final SEM for the directional relationships between cognitions, anxiety, and diabetes self-care. Five pathways were statistically significant using an alpha of 0.05. Figure 3 shows that individuals who were more concerned about their diabetes at baseline had greater symptoms of anxiety at six months. Thus indicating a direct effect of cognitions (explanatory variable) on anxiety (mediator variable). However because a pathway leading from baseline anxiety (mediator variable) to diabetes self-care (outcome variable) at six months follow-up is absent, Cole and Maxwell’s (2003) step two criteria for establishing longitudinal mediation for the cognition → emotion → diabetes self-care pathway was not supported. Conversely, individuals who were more anxious at baseline had higher beliefs in the unpredictable nature of diabetes (timeline cyclical), attributed greater importance to their diabetes medications for managing their condition (medication necessity), and had greater concerns about the potential consequences of their diabetes medications (medication concerns). Thus demonstrating the direct effect of anxiety (explanatory variable) on cognitions (mediator variables) and met Cole and Maxwell’s (2003) step one criteria for the initial part of the emotion → cognition → diabetes self-care pathway. However because Figure 3 does not include any directional pathways leading from baseline timeline cyclical, medication necessity, and medication concerns to diabetes self-care the effect of the mediator (cognitions) on the outcome (diabetes self-care) was not supported. Consistent with the depression model, baseline personal control beliefs acted independently of emotions to influence the degree of adherence to diabetes self-care at six months follow-up.

We evaluated the overall model fit of all of the directional pathways included in our anxiety model, using model fit indices and criteria described in Table 1. The model shown in Figure 3, had evidence of good statistical fit on all fit indices, excluding the model chi-square statistic (χ²=57.45, dfm=40, p=.04; RMSEA=.04, CFI=.97, SRMR=.05, N=153).

[INSERT FIGURE 3 HERE]

### *Potential confounders*

In both models the statistical significance of directional pathways remained unchanged after controlling for potential confounders, with three exceptions. In both models the directional pathway leading from baseline personal control to diabetes self-care became statistically non-significant when number of diabetes complications was added as a covariate. Specifically for the depression model, baseline depression scores did not explain variance in the timeline cyclical cognition at six months, after controlling for diabetes treatment regimen. Similarly, for anxiety, the directional pathway from baseline medication concerns to anxiety at six months follow-up was not significant when diabetes duration was controlled for.

# Discussion

 This is the first study to simultaneously examine directional relationships between cognitions, emotions, and diabetes self-care in an outpatient type 2 diabetes population. Our findings support our theoretically driven hypothesis that cognitions have direct effects on diabetes self-care. Indeed, we found that personal control beliefs operated independently of emotions to influence adherence to diabetes self-care over time. However contrary to our hypothesis about the nature of this relationship, we found that individuals who felt more confident in their ability to self-manage their diabetes actually adhered less to their diabetes self-care treatments over time. Furthermore, this effect was not sustained once number of diabetes complications was added as a covariate to both the depression and anxiety models.

 Consistent with the CS-SRM ([Leventhal et al., 1980](#_ENREF_28)) and CBT treatment models ([Beck et al., 1979](#_ENREF_7)), we identified a reciprocal relationship between cognitions and emotions. Diabetes medication concerns had a longitudinal effect on depressive and anxious symptoms. Equally higher levels of depression and anxiety influenced diabetes cognition domains over time, specifically: timeline cyclical, medication necessity (anxiety only), and medication concerns (anxiety only). These relationships identify potentially salient mechanisms to target when managing negative emotions in the context of Type 2 diabetes. However, contrary to our hypotheses, our findings did not support the combined effects of these cognition-emotion pathways on diabetes self-care. More specifically negative emotions had no direct effect on diabetes self-care. Despite finding that medication concerns increased both depressive and anxious symptoms over time, neither depression nor anxiety mediated the effect of medication concerns on diabetes self-care, as indicated by these pathways being absent from the models. Conversely, we found no evidence to support the hypothesis that diabetes cognitions mediate the effect of depression and anxiety on diabetes self-care. Although we identified an explanatory effect of depression and/or anxiety on three illness cognition domains over time, none of these domains demonstrated associations with diabetes self-care.

## *Strengths and limitations*

Our study used a longitudinal design, thus our findings about the directional relationships in the models are robust ([Kenny, 1979](#_ENREF_26)). A relatively large sample was recruited (n=261) of which 73.3% (n=194) were retained at six months follow-up. A quarter of our sample were individuals from black and minority ethnic groups, making it representative of the wider UK diabetes outpatient population. The use of SEM enabled multiple pathways to be modelled simultaneously, yielding a more valid representation of the competing relationships between cognitions, emotions, and diabetes self-care ([Kline, 2005](#_ENREF_27)) and allowed a theoretically driven approach to our analyses. The validity of our findings is bolstered further due to confirmation that observed directional pathways between variables remained unchanged when potential demographic and clinical confounders were accounted for, excluding the confounding roles of diabetes complications, diabetes duration, and medication type - the implications of which are discussed below.

 Limitations of our study include a relatively short follow up period, which may have prevented the detection of important associations. Participants’ health in this study was likely stable given their mean diabetes duration of 14 years and because they were recruited from ambulatory outpatient clinics as opposed to settings that care for more severely ill patients. The temporal relationships that exist between illness cognitions, emotions, and diabetes self-care are largely unknown. There may be critical incidents in a person’s diabetes illness trajectory that trigger change (e.g. complication onset), but to measure this would require approaches with much longer follow-up intervals. Relatedly, this study was limited to two data collection time points, which prevented the full testing of theoretically driven indirect pathways across three time points. We attempted to overcome this issue by implementing the Cole and Maxwell (2003) two-step procedure, which allowed us to test each hypothesised directional pathway longitudinally. However, we need to be mindful that our findings from our hypothesised mediators to diabetes self-care may not accurately reflect relationships that could have occurred had we been able to obtain data from a third follow-up time point. Second, because this study was exploratory, specifically in relation to identifying the longitudinal cognition-emotion profiles relevant to a Type 2 diabetes outpatient population, we did not want to discount potentially important relationships ([Rothman, 1990](#_ENREF_39)), so no adjustments for multiple testing (bonferroni corrections) were made.

## *What are the combined effects of negative emotions and illness cognitions on self-care in adults with type 2 diabetes?*

Our findings have identified that illness cognitions can remain independent of emotions and have directional effects on diabetes self-care. Contrary to previous cross-sectional findings showing an association between high levels of confidence in personal capabilities for managing diabetes (personal control) and improved adherence ([Broadbent et al., 2011](#_ENREF_9); [Watkins et al., 2000](#_ENREF_45)); our findings showed that patients who felt more confident in their ability to manage diabetes demonstrated *reduced* adherence to their diabetes self-care behaviours over time. The mean diabetes duration of our sample was 14 years, therefore participants may have developed automatic habitual coping behaviours for managing diabetes, consistent with findings in hypertension, where habit strength was the strongest predictor of adherence ([Phillips, Leventhal, & Leventhal, 2013](#_ENREF_37)). Participants in our sample possibly felt confident in undertaking their day-to-day diabetes management routines, but these routines likely deviated from the recommendations of health care professionals, identifying the need for regular reviews of diabetes self-care behaviours during clinical consultations. The role of clinical confounders warrants attention. The directional effect of personal control on diabetes self-care was no longer statistically significant when number of diabetes complications was included as a covariate in both the depression and anxiety models. This finding may not be surprising given that the presence of diabetes related complications has been identified as a key motivator for change in diabetes self-care behaviours ([van Puffelen et al., 2015](#_ENREF_43)). This has important clinical implications about how we can support the *prevention* of future diabetes complications and identified the need to harness patients personal control beliefs effectively using intervention techniques such as motivational interviewing ([Miller & Rollnick, 2012](#_ENREF_32)).

Our study reinforces the claims of the CS-SRM ([Leventhal et al., 1980](#_ENREF_28)) and highlights the salience of reciprocal relationships between cognitions and emotions, which can contribute to the maintenance and exacerbation of depression and anxiety in diabetes. Consistent with cognitive-behavioural therapy ([Beck, 1964](#_ENREF_5)) and our hypotheses, having a pessimistic appraisal of diabetes treatments heightened participant’s experience of depression and anxiety over time. But equally depression and anxiety influenced participants beliefs about diabetes in a pessimistic manner, likely occurring because of altered attentional control processes in response to arousal ([Cameron, 2003](#_ENREF_10)). In heightened states of arousal attention can become focussed on somatic symptom detection, thus a person’s diabetes cognitive illness representation is updated in response to identified somatic changes. But equally mood may be unhelpfully used as a heuristic for physical heath ([Leventhal et al., 1980](#_ENREF_28)). Somatic symptoms of depression and anxiety (including shaking, sweating, low energy) overlap with symptoms of hypoglycaemia, thus leading to the misattribution of physical symptoms provoked by emotions, to diabetes. The longitudinal relationships observed in our study between cognitions and emotions are largely consistent with cross-sectional findings ([Hudson et al., 2014](#_ENREF_22)). However we did not identify longitudinal associations between increased perceived consequences and poorer emotional health and likewise lower perceptions of personal control and poorer emotional health, despite cross-sectional studies consistently reporting these effects ([Hudson et al., 2014](#_ENREF_22)).

It is important to acknowledge that depression made no statistically significant contribution to the timeline cyclical cognition domain when modelled alongside a person’s diabetes medication treatment regimen. The intensity of a person’s medication regimen varies as a function of their degree of blood glucose dysregulation. Thus it is plausible that individuals with poorer blood glucose control who as a result are prescribed more intensive diabetes medication regimens experience greater levels of depression. As such diabetes treatment regimens have the potential to moderate the degree of depression experienced and ultimately the extent to which this goes on to influence a person’s appraisal of their diabetes in a moderated-mediation pathway. In addition, the explanatory effect of medication concerns on anxiety became statistically non-significant when diabetes duration was included as a model covariate. Consistent with the CS-SRM, it is likely that individuals with a longer diabetes duration have developed effective coping strategies for managing their threatening diabetes medication perceptions and thus have emotionally adjusted to these concerns. As such it is important to consider how salient mechanisms of action within CS-SRM differ depending on the context of a person’s illness trajectory (e.g. newly diagnosed vs stable condition).

Whilst our findings identified the importance of reciprocal relationships between cognitions and emotions, the absence of their combined effects on diabetes self-care is surprising and contrary to our research hypotheses. Among individuals who are experiencing more severe symptoms of depression and anxiety, these cognition-emotion pathways and vice versa, may well go on to influence diabetes self-care behaviour. Indeed, it is worthy to note, that these relationships were identified in our study, when neither emotions nor cognitions were explicitly manipulated. Thus the degree of explanatory effects is attenuated. In addition participants in our sample showed relatively low levels of depression and anxiety symptoms, which may at least partly account for our null findings. Previous studies that have shown a relationship between depression and diabetes outcomes over time have included clinically depressed populations ([Dirmaier et al., 2010](#_ENREF_13); [Katon et al., 2010](#_ENREF_25); [Lin et al., 2004](#_ENREF_29)). Nonetheless, our sample’s mean levels of depression and anxiety are consistent with others who have used the DWBQ in people with Type 2 diabetes ([French et al., 2008](#_ENREF_14); [Paschalides et al., 2004](#_ENREF_36)), and thus can be considered representative of a general diabetes outpatient population.

***Clinical implications***

Psychological interventions to date that have addressed depression and anxiety in the context of diabetes have improved mental health outcomes but corresponding achievements in diabetes health outcomes (HbA1c) are lacking ([Harkness et al., 2010](#_ENREF_20)). By testing the CS-SRM longitudinally a comprehensive model the illness specific cognitive-behavioural pathways through which depression and anxiety operate in the context of diabetes can be developed. This will allow the development of modified interventions that better integrate the management of physical and mental health, a priority identified for health care commissioners ([Imison et al., 2011](#_ENREF_24)), whilst also decreasing the burden of care for patients with multimorbidity ([Mercer et al., 2012](#_ENREF_31)). Cognitive-behavioural therapy ([Beck, 1976](#_ENREF_6)) is a treatment that can target the causal mechanisms outlined in the CS-SRM. Our study should be replicated in a larger sample with moderation analyses to compare cognition, emotion, and behavioural outcome profiles among people who meet diagnostic thresholds for depression and/or anxiety with those who do not. This will help to isolate pathways that need to be addressed in self-management interventions based on patient clinical presentations and will lead to the development of more personalised and efficient psychological medicine.

**Acknowledgements**

The study was funded by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care Greater Manchester at Salford Royal NHS Foundation Trust. Chris Dickens is funded by the NIHR CLAHRC for the South West Peninsula (UK). The funders had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; and the preparation, review, or approval of the manuscript. The views expressed in this article are those of the authors and not necessarily the NIHR, the NHS, or the Department of Health.

**Conflicts of Interests:** None

**Author contributions:** Study design: JH, CB, PC, CD, DR; study management: JH; statistical analysis: DR, AW; JH. All authors contributed to writing the manuscript.

**References**

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The prevalence of comorbid depression in adults with diabetes - A meta-analysis. *Diabetes Care, 24*(6), 1069-1078.

Arbuckle, J. (2007). *AMOS 16.0 User's Guide*. Chicago: Amos Development Corporation, SPSS Inc.

Barnes, L., Moss-Morris, R., & Kaufusi, M. (2004). Illness beliefs and adherence in diabetes mellitus: a comparison between Tongan and European patients. *The New Zealand medical Journal, 117*(1188), 743-751.

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and social Psychology, 51*(6), 1173.

Beck, A. T. (1964). Thinking and depression: II. Theory and Therapy. *Archives of General Psychiatry, 10*, 561-571.

Beck, A. T. (1976). *Cognitive therapy and the emotional disorders*. New York: Penguin Group.

Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive therapy of depression*. New York: The Guilford Press.

Bradley, C. (1994). The Well-being Questionnaire. In C. Bradley (Ed.), *Handbook of Psychology and Diabetes* (pp. 89-109). Berkshire: Harwood Academic Press.

Broadbent, E., Donkin, L., & Stroh, J. C. (2011). Illness and treatment perceptions are associated with adherence to medications, diet, and exercise in diabetic patients. *Diabetes Care, 34*(2), 338-340.

Cameron, L. (2003). Anxiety, cognition, and responses to healh threats. In L. Cameron & H. Leventhal (Eds.), *The self-regulation of health and illness behaviour* (Vol. 1, pp. 157-183). New York Routledge.

Cole, D. A., & Maxwell, S. E. (2003). Testing mediational models with longitudinal data: questions and tips in the use of structural equation modeling. *Journal of Abnormal Psychology, 112*(4), 558-577.

de Groot, M., Anderson, R., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). Association of depression and diabetes complications: A meta-analysis. *Psychosomatic Medicine, 63*(4), 619-630.

Dirmaier, J., Watzke, B., Koch, U., Schulz, H., Lehnert, H., Pieper, L., & Wittchen, H. U. (2010). Diabetes in primary care: prospective associations between depression, nonadherence and glycemic control. *Psychotherapy and psychosomatics, 79*(3), 172-178.

French, D., Wade, A. N., Yudkin, P., Neil, H. A. W., Kinmonth, A. L., & Farmer, A. J. (2008). Self-monitoring of blood glucose changed non-insulin-treated Type 2 diabetes patients' beliefs about diabetes and self-monitoring in a randomized trial. *Diabetic Medicine, 25*(10), 1218-1228.

Gonzalez, J. S., Peyrot, M., McCarl, L. A., Collins, E. M., Serpa, L., Mimiaga, M. J., & Safren, S. A. (2008). Depression and Diabetes Treatment Nonadherence: A Meta-Analysis. *Diabetes Care, 31*(12), 2398-2403. doi: 10.2337/dc08-1341

Grigsby, A. B., Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2002). Prevalence of anxiety in adults with diabetes - A systematic review. *Journal of psychosomatic research, 53*(6), 1053-1060.

Hagger, M. S., & Orbell, S. (2003). A meta-analytic review of the common-sense model of illness representations. *Psychology & Health, 18*(2), 141-184.

Hampson, S. E., Glasgow, R. E., & Foster, L. S. (1995). Personal Models of Diabetes Among Older Adults: Relationship to Self-Management and Other Variables. *The Diabetes Educator, 21*(4), 300-307. doi: 10.1177/014572179502100407

Hampson, S. E., Glasgow, R. E., & Toobert, D. J. (1990). Personal models of diabetes and their relations to self-care activities. *Health Psychology, 9*(5), 632-646.

Harkness, E., Macdonald, W., Valderas, J., Coventry, P., Gask, L., & Bower, P. (2010). Identifying Psychosocial Interventions That Improve Both Physical and Mental Health in Patients With Diabetes A systematic review and meta-analysis. *Diabetes Care, 33*(4), 926-930.

Horne, R., Weinman, J., & Hankins, M. (1999). The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology & Health, 14*(1), 1-24.

Hudson, J., L, Bundy, C., Coventry, P., A, & Dickens, C. (2014). Exploring the relationship between cognitive illness representations and poor emotional health and their combined association with diabetes self-care. A systematic review with meta-analysis. *Journal of psychosomatic research, 76*(4), 265-274.

IBM SPSS Statistics. (2010). *IBM SPSS Statistics for Windows, Version 19*. Armonk, NY: IBM Corp.

Imison, C., Naylor, C., Buck, D., Curry, N., Addicott, R., & Zollinger-Read, P. (2011). Transforming our healthcare system. *London: The King’s Fund*.

Katon, W. J., Russo, J. E., Heckbert, S. R., Lin, E. H. B., Ciechanowski, P., Ludman, E., . . . Von Korff, M. (2010). The relationship between changes in depression symptoms and changes in health risk behaviors in patients with diabetes. *International journal of geriatric psychiatry, 25*(5), 466-475. doi: 10.1002/gps.2363

Kenny, D. A. (1979). Correlation and causality. *New York: Wiley, 1*.

Kline, R. B. (2005). *Principles and Practice of Structural Equation Modelling.* New York: The Guildford Press.

Leventhal, H., Meyer, D., & Nerenz, D. R. (1980). The Common Sense Model of Illness Danger. In S. Rachman (Ed.), *Medical Psychology* (Vol. 2, pp. 7-30). New York: Pergamon.

Lin, E. H. B., Katon, W., Von Korff, M., Rutter, C., Simon, G. E., Oliver, M., . . . Young, B. (2004). Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care, 27*(9), 2154-2160.

Lustman, P. J., Anderson, R. J., Freedland, K. E., de Groot, M., Carney, R. M., & Clouse, R. E. (2000). Depression and poor glycemic control - A meta-analytic review of the literature. *Diabetes Care, 23*(7), 934-942.

Mercer, S. W., Gunn, J., Bower, P., Wyke, S., & Guthrie, B. (2012). Managing patients with mental and physical multimorbidity. *Bmj, 345*(sep03 1), e5559-e5559.

Miller, W. R., & Rollnick, S. (2012). *Motivational interviewing: Helping people change*: Guilford press.

Mooney, C. Z., & Duval, R. D. (1993). *Bootstrapping. A nonparametric approach to statistical inference.* London: Sage Publications Inc.

Moss-Morris, R., Weinman, J., Petrie, K. J., Horne, R., Cameron, L. D., & Buick, D. (2002). The revised Illness Perception Questionnaire (IPQ-R). *Psychology & Health, 17*(1), 1-16.

Park, M., Katon, W. J., & Wolf, F. M. (2013). Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. *General hospital psychiatry, 35*(3), 217-225.

Paschalides, C., Wearden, A., Dunkerley, R., Bundy, C., Davies, R., & Dickens, C. (2004). The associations of anxiety, depression and personal illness representations with glycaemic control and health-related quality of life in patients with type 2 diabetes mellitus. *Journal of psychosomatic research, 57*(6), 557-564. doi: <http://dx.doi.org/10.1016/j.jpsychores.2004.03.006>

Phillips, L. A., Leventhal, H., & Leventhal, E. A. (2013). Assessing Theoretical Predictors of Long-Term Medication Adherence: Patients' Treatment-Related Beliefs, Experiential Feedback, and Habit Development. *Psychology & Health, In press*.

Pincus, T., Griffiths, J., Isenberg, D., & Pearce, S. (1997). The WellBeing Questionnaire: Testing the structure in groups with rheumatoid arthritis. *British journal of health psychology, 2*(2), 167-174.

Rothman, K. J. (1990). No adjustments are needed for multiple comparisons. *Epidemiology, 1*(1), 43-46.

Rustad, J. K., Musselman, D. L., & Nemeroff, C. B. (2011). The relationship of depression and diabetes: Pathophysiological and treatment implications. *Psychoneuroendocrinology, 36*(9), 1276-1286.

Searle, A., Norman, P., Thompson, R., & Vedhara, K. (2007). A prospective examination of illness beliefs and coping in patients with type 2 diabetes. *British journal of health psychology, 12*, 621-638. doi: 10.1348/135910706x164935

Toobert, D. J., Hampson, S. E., & Glasgow, R. E. (2000). The summary of diabetes self-care activities measure - Results from 7 studies and a revised scale. *Diabetes Care, 23*(7), 943-950.

van Puffelen, A. L., Heijmans, M. J., Rijken, M., Rutten, G. E., Nijpels, G., & Schellevis, F. G. (2015). Illness perceptions and self-care behaviours in the first years of living with type 2 diabetes; does the presence of complications matter? *Psychology & Health*(just-accepted), 1-24.

Walker, R. J., Gebregziabher, M., Martin-Harris, B., & Egede, L. E. (2015). Understanding the influence of psychological and socioeconomic factors on diabetes self-care using structured equation modeling. *Patient education and counseling, 98*(1), 34-40. doi: <http://dx.doi.org/10.1016/j.pec.2014.10.002>

Watkins, K. W., Connell, C. M., Fitzgerald, J. T., Klem, L., Hickey, T., & Ingersoll-Dayton, B. (2000). Effect of adults' self-regulation of diabetes on quality-of-life outcomes. *Diabetes Care, 23*(10), 1511-1515.

World Health Organization. (2010). International Statistical Classification of Diseases and Related Health Problems 10th Revision. Retrieved 15 May, 2013, from <http://apps.who.int/classifications/icd10/browse/2010/en>

Zung, W. W. (1974). The measurement of affects: depression and anxiety. *Modern Problems of Pharmacopsychiatry, 7*, 170-188.

Zung, W. W., Richards, C. B., & Short, M. J. (1965). Self-Rating Depression Scale in an Outpatient Clinic: Further Validation of the SDS. *Archives of General Psychiatry, 13*(6), 508-515. doi: 10.1001/archpsyc.1965.01730060026004

**Table 1: Goodness of Fit Indices used to evaluate models**

|  |  |
| --- | --- |
| Goodness of fit index | Statistical interpretation |
| Model chi-square χ² | Smaller χ² = better model fit. Requires a true null hypothesis.  |
| Comparative Fit Index (CFI) | Values close to 0.95 indicate a good fit.  |
| Root Mean Square Error of Approximation (RMSEA) | Values ≤ 0.06 indicate good fit.  |
| Standardised Root Mean Square Residual (SRMR) | Values ≤0.10 indicate good fit. |

**Table 2: Demographic and clinical characteristics of participants at 6 months follow-up**

|  |  |  |
| --- | --- | --- |
| Variable | Mean/Frequency | Standard Deviation/Percentage  |
| Gender | Male | 120 | 61.9 |
|  | Female | 74 | 38.1 |
|  |  |  |  |
| Age/years | mean | 62.8 | 11.9 |
|  | median | 63.0 | 55.0-72.0 |
| Ethnicity | White | 140 | 72.2 |
|  | Black | 25 | 12.9 |
|  | Asian | 24 | 12.4 |
|  | Mixed race | 4 | 2.1 |
|  | Other/prefer not to say | 1 | 0.52 |
| Diabetes duration/years | mean | 14.3 | 8.8 |
|  | median | 13.0 | 8.3-19.0 |
| Diabetes treatment regimen | Diet/oral hypoglycaemics | 53 | 27.3 |
|  | Injections/Combination  | 128 | 66.0 |
|  | No access to medical records/missing data  | 13 | 6.7 |
|  |  |  |  |
| Clinical outcomes |  |  |  |
| HbA1c mmol/mol |  | 65.6 | 16.7 |
| Number of complications |  | 2.0 | 1.2 |
| Number of other co-morbidities |  | 1.5 | 1.2 |

**Table 3: Follow-up scores on self-report measures of depression, anxiety, diabetes cognitions, and diabetes self-care**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables |   | Mean | Standard Deviation | Cronbach’s alpha |
| ***Well-being questionnaire***  |  |
| Depression |  | 4.7 | 3.6 | 0.84 |
| Anxiety |  | 5.4 | 4.2 | 0.83 |
| **Illness Perception Questionnaire-Revised**  |  |
| Identity |  | 3.8 | 3.2 | 0.77 |
| Timeline acute/chronic |  | 4.2 | 0.7 | 0.73 |
| Timeline cyclical |  | 2.9 | 1.0 | 0.82 |
| Consequences |  | 3.3 | 0.8 | 0.80 |
| Personal control |  | 4.0 | 0.7 | 0.77 |
| Treatment control |  | 3.6 | 0.6 | 0.53 |
| Illness coherence |  | 3.6 | 0.9 | 0.90 |
| Emotional representations |  | 2.7 | 1.0 | 0.88 |
| ***Beliefs about Medicines Questionnaire*** |  |  |  |
| Medication necessity |  | 4.1 | 0.8 | 0.89 |
| Medication concerns |  | 2.8 | 1.0 | 0.80 |
| ***Summary of diabetes self-care activity scale***  |  |
| General diet |  | 5.0 | 2.1 | 0.92 |
| Specific diet (fruit & veg) |  | 4.7 | 2.3 | Single item NA |
| Specific diet (saturated fat) |  | 4.5 | 2.0 | Single item NA |
| Exercise |  | 2.3 | 2.3 | 0.79 |
| Self-monitoring of blood glucose |  | 4.6 | 2.7 | 0.90 |
| Foot care |  | 3.7 | 2.6 | 0.65 |
| Medication adherence |  | 6.8 | 0.9 | Single item NA |
| Global diabetes self-care |  | 3.9 | 1.3 | 0.62 |
|  |  |  |  |  |

**Figure headings and captions**

**Figure 1: Flow chart of participants recruited and retained at each stage of the study**



**Figure 2: Final model of the simultaneous effect of cognitions and depression on diabetes self-care**



**Figure 3: Final model of the simultaneous effect of cognitions and anxiety on diabetes self-care**

****

**Figure captions:**

***Figure 1:*** Recruitment and retention flow diagram

***Figure 2 & 3*:** Statistics reported next to directional arrows are standardised regression coefficients. Those aligned left refer to auto-regressive pathways. Those aligned right refer to directional pathways. Statistics adjacent to outcome variable detail the percentage variance explained. All baseline variables were specified to correlate with each other.

Key: \*p≤0.05, \*\*p≤0.01, \*\*\*, p≤0.001