

## RESEARCH ARTICLE

# Relationship between Type D personality and adverse health outcomes in people with type 2 diabetes: The parallel mediating roles of diabetes distress and social isolation

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## Abstract

**Aim:** To investigate the relationship between Type D personality and adverse health outcomes [glycated haemoglobin (HbA1c) and health-related quality of life (HRQOL)] directly, and indirectly via diabetes distress and social isolation in people with type 2 diabetes.

**Design:** A secondary analysis of 524 participant's data derived from a cross-sectional, correlational study with people with type 2 diabetes.

**Methods:** Data were analysed using the PROCESS macro of SPSS.

**Results:** Type D personality was present in 31.3% of the participants, and exerted a direct effect on HRQOL but not on HbA1c. Type D personality indirectly affected both HbA1c and HRQOL via the mediators of diabetes distress and social isolation. Nurses need to monitor people with type 2 diabetes to determine whether Type D personality is present. Those with Type D personality should be provided with interventions to reduce diabetes distress and alleviate social isolation in order to improve HbA1c and HRQOL.

## KEYWORDS

diabetes, distress, glycated haemoglobin, health-related quality of life, mediation, personality, social isolation

## 1 | INTRODUCTION

Type D (or 'distressed') personality is characterized by the combination of two constant personality traits: negative affectivity (NA) and social inhibition (SI) (Denollet, 2005). NA is the tendency to experience negative emotions, and SI is the tendency to inhibit self-expression during social interactions (Denollet, 2000). Although Type D personality originally emerged as a risk factor for adverse health outcomes in people with coronary health diseases, it has since also been recognized as a risk factor for people with other medical conditions (Mols &

Denollet, 2010a). However, there is insufficient evidence for its relationship among people with type 2 diabetes (Shao et al., 2017).

### 1.1 | Background

According to the American Diabetes Association and European Association for the Study of Diabetes, the goals of type 2 diabetes treatment are to control blood glucose to prevent or delay complications, and to maintain the quality of life (Davies et al., 2018).

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Glycated haemoglobin (HbA1c) is a standard objective marker of blood glucose control and reflects average blood glucose levels over 2–3 months (The International Expert Committee, 2009). The term 'quality of life' is a concept that is too broad since it includes welfare, economic situations and health statuses; however, health-related quality of life (HRQOL) is considered a more concise indicator to determine outcomes in clinical situations (Fayers & Machin, 2016). From these perspectives, HbA1c and HRQOL can represent outcome parameters for type 2 diabetes. Negative associations can therefore be assumed between Type D personality and diabetes outcomes such as HbA1c and HRQOL.

A few studies have been conducted on Type D personality in people with type 2 diabetes even at early stages (Conti et al., 2016). However, the previous studies that examined the relationship between Type D personality and HbA1c in people with type 2 diabetes produced inconsistent findings, with some indicating that people with Type D personality had a greater risk of high HbA1c levels (Conti et al., 2017; Lin et al., 2020; Shao et al., 2017), while another indicating no direct association and hence suggesting the need to explore its indirect effects via mediators (Nefs et al., 2015).

People with Type D personality and a long-term disease, particularly cardiovascular disease, have been reported to experience greater impairments in their HRQOL (Aquarius et al., 2007; Jo et al., 2019; Staniute et al., 2015). However, this relationship among people with diabetes has rarely been investigated. Conti et al. (2017) were the first and are still the only authors to empirically demonstrate this relationship among people with type 2 diabetes.

The mechanisms that underlie the associations between Type D personality and adverse clinical outcomes are currently unclear (Huang et al., 2017). It is, therefore, necessary to determine which factors mediate the adverse effects of Type D personality on health outcomes (Staniute et al., 2015). Psychosocial factors have been conjectured to be plausible mediators of these mechanisms (Williams et al., 2008).

Diabetes distress refers to negative emotions experienced in response to the burden of living with and managing diabetes (Fisher et al., 2012; Gonzalez et al., 2011). A previous study with people with type 2 diabetes showed that those with Type D personality had greater feelings of distress from diabetes (Nefs et al., 2012). Greater diabetes distress has been suggested to worsen blood glycaemic control (Asuzu et al., 2017; Fisher et al., 2010) and reduce HRQOL in people with type 2 diabetes (Carper et al., 2014; Jannoo et al., 2017; Wang et al., 2021). Together these findings suggest that the relationships of Type D personality with HbA1c and HRQOL could be mediated by diabetes distress.

Another plausible pathway for how Type D personality predicts adverse diabetes outcomes is via social isolation, which is characterized by a lack of contact with others and social involvement (Shankar et al., 2011). An association has been reported between Type D personality and social isolation among both people with cardiovascular disease and those from a general population (Michal et al., 2011; Rashidi et al., 2017). Social isolation is known to have an association with HbA1c in people with diabetes (Ida et al., 2020), and to

be negatively related to HRQOL among elders (Beridze et al., 2020; Hawton et al., 2011). Accordingly, Type D personality can be postulated to have an association with social isolation, which in turn could be related to adverse HbA1c and HRQOL outcomes in people with type 2 diabetes.

If two or more mediators linked by the same independent and outcomes variables are weakly correlated with each other or not based on causality, they are parallel mediators (Hayes, 2018). Since no causal evidence exists between the diabetes distress and social isolation mediators, they are expected to be parallel mediators in the association between Type D personality and the diabetes outcomes of HbA1c and HRQOL.

## 1.2 | Aims

In this study, we aimed to investigate the relationship between Type D personality and adverse outcomes (HbA1c and HRQOL) directly, and also indirectly via parallel mediators (diabetes distress and social isolation) in people with type 2 diabetes. The following two hypotheses were tested:

**Hypothesis 1.** Type D personality is related to HbA1c directly and also indirectly related via diabetes distress and social isolation in people with type 2 diabetes.

**Hypothesis 2.** Type D personality is related to HRQOL directly and also indirectly related via diabetes distress and social isolation in people with type 2 diabetes.

## 2 | METHODS

### 2.1 | Design and participants

This study used a correlational design to conduct a secondary analysis of data derived from a large survey of adults with type 2 diabetes recruited from June 2020 to February 2021 at multi-outpatient clinics (Lee et al., 2021). The original survey was performed to explore the relationship of health literacy to diabetes self-management. The present study explored the relationship between Type D personality and adverse health outcomes (HbA1c and HRQOL). The general and medical information were presented in greater detail elsewhere (Lee et al., 2021). The sample size of 524 cases satisfied the requirement for the statistical power of 0.80 at the significance level of 0.05 to validate the indirect effects of this study (Fritz & MacKinnon, 2007).

### 2.2 | Measurements

#### 2.2.1 | Type D personality

Type D personality was identified using the 14-item Type D scale (DS14), which consists of two 7-item subscales measuring NA and SI (Denollet, 2005). Each item is scored on a 5-point rating scale

ranging from 0 to 4, with the scores of each subscale ranging from 0 to 28. Cronbach's alpha values in the original study were 0.88 and 0.86 for NA and SI, respectively, and test-retest reliability coefficients were 0.72 and 0.82 respectively. The DS14 has been validated in various populations, including people with type 2 diabetes (Nefs et al., 2012) and Koreans (Lim et al., 2011). Cronbach's alpha values in the present study for NA and SI were 0.86 and 0.78 respectively. Type D personality was categorized using a criterion of  $\geq 10$  points on both the NA and SI subscales.

### 2.2.2 | Diabetes distress

Diabetes distress was measured using a 5-item short-form version of the Problem Areas in Diabetes (PAID-5) (McGuire et al., 2010) scale derived from the original 20-item version of PAID (Polonsky et al., 1995). Each item is scored on a 5-point Likert scale from 'not a problem' to 'a serious problem'. The PAID-5 has possible scores ranging from 0 to 20, with higher scores indicating greater diabetes-related distress. The Korean version of the PAID-5 had satisfactory factorial structural, convergent and known-groups validities, internal consistency (Cronbach's alpha = 0.87) and test-retest reliability (intraclass correlation coefficient = 0.89) among 440 people with type 2 diabetes (Lee et al., 2014). Cronbach's alpha of the Korean version was 0.91 in the present study.

### 2.2.3 | Social isolation

Social isolation was measured using the 5-item Social Isolation Index (Shankar et al., 2011), which determines whether a respondent (i) is not married/not cohabiting with a partner; (ii) does not participate in any organization, religious group or committee; and has less than monthly contact with (iii) friends, (iv) relatives and (v) other family members they do not live with (including face-to-face, telephone or written/e-mail contact). The scores of this index ranged from 0 to 5, with higher scores indicating greater social isolation.

### 2.2.4 | Glycated haemoglobin

The level of HbA1c, which is an integrated marker of glycaemic control, was collected from the medical records of the participants.

### 2.2.5 | Health-related quality of life

The Diabetes-Specific Quality of Life (D-QOL) was used to measure HRQOL and consisted of 16 items that were responded to on a 5-point Likert scale (Lee et al., 2012). All items were reversed and averaged to ensure that higher scores indicated better HRQOL. The D-QOL demonstrated satisfactory content, factorial construct (using exploratory and confirmatory factor analyses),

concurrent and known-groups validities and internal consistency (Cronbach's alpha = 0.92) among 402 people with type 2 diabetes (Lee et al., 2012). Cronbach's alpha of the D-QOL was 0.91 in the present study.

## 2.3 | Data analysis

Data were analysed using SPSS (version 25.0 for Windows) and its PROCESS macro (version 3.5.3). Study variables were computed using descriptive statistics. Pearson's correlation analysis, *t*-tests and ANOVAs were performed to identify any covariates between the general characteristics of participants and the mediator/outcome variables (diabetes distress, social isolation, HbA1c and HRQOL). The covariates were the general characteristics associated with both mediators and outcome variables (Hayes, 2018). Statistical assumptions of the multiple regression were determined before the mediation analysis. Multicollinearity among predictive variables was determined using the variance inflation factor (VIF). The Durbin-Watson statistic was computed to determine if the residuals from the multiple regression analysis were independent. Assumptions of linearity and homoscedasticity were determined using a plot of standardized residuals versus standardized predicted values (Hayes, 2018; Tabachnick & Fidell, 2019). The hypotheses of this study were analysed using the PROCESS macro (Hayes, 2018) which was used to estimate the 95% confidence intervals (CIs) of indirect effects, based on 10,000 bootstrapped samples. An indirect effect was considered statistically significant when its 95% CI did not include zero. Indirect-effect values were quoted to three decimal places.

## 2.4 | Ethical consideration

Research ethics committee approval was obtained from the institutional review boards (approval numbers 'REDACTED'). All participants signed informed consents before data collection.

## 3 | RESULTS

### 3.1 | Preliminary analyses

Among the 524 participants included, 164 (31.3%) were categorized as Type D personality. The mean scores for diabetes distress, social isolation, HbA1c and HRQOL were 8.38 (SD = 5.29), 1.07 (SD = 1.03), 7.30 (SD = 1.27) and 2.96 (SD = 0.75) respectively. Diabetes distress had a weak correlation with social isolation ( $r = 0.10$ ,  $p < 0.015$ ).

In the assumption tests, the VIF values for all predictive variables were  $< 10$  for the HbA1c (1.04–1.12) and HRQOL (1.04–1.12) outcome variables, indicating a low redundancy among them. The values of the Durbin-Watson statistic were near 2 (1.92 and 1.90 for HbA1c and HRQOL, respectively) for the independent residuals of the dependent

variables, indicating the absence of autocorrelation. The plot of standardized residuals versus standardized predicted values for HbA1c and HRQOL indicated satisfactory linearity (the LOESS curves centred along the entire X axis were close to 0) and homoscedasticity (all data on the plot were consistently and equally spread on the Y axis).

No covariates among the general characteristics were found to be associated with both mediators and HbA1c. However, females had statistically significantly higher diabetes distress scores ( $t = -3.93, p < 0.001$ ) and lower HRQOL scores ( $t = 2.63, p = 0.010$ ) than males. Moreover, the participants with higher education levels (high school and above) had statistically significantly lower isolation scores ( $t = 3.05, p = 0.002$ ) and higher HRQOL scores ( $t = 2.96, p = 0.003$ ) than did those who had only graduated from elementary or middle school (Table S1). Gender and education level were therefore included as covariates in the subsequent parallel mediation model linking Type D personality and HRQOL.

### 3.2 | Hypothesis 1

Figure 1 (and Table S2) indicates that Type D personality statistically significantly predicted both diabetes distress ( $a_1 = 3.314, p < 0.001$ ) and social isolation ( $a_2 = 0.397, p < 0.001$ ). HbA1c exhibited statistically significant regression with diabetes distress ( $b_1 = 0.026, p = 0.021$ ) and social isolation ( $b_2 = 0.136, p = 0.013$ ) when other variables were kept constant. However, the direct effect of Type D personality on HbA1c ( $c' = 0.062$ ) was insignificant when controlling for diabetes distress and social isolation ( $p = 0.622$ ).

Table 1 indicates that there was a statistically significant indirect effect of Type D personality on HbA1c via diabetes distress when controlling for social isolation ( $a_1 \times b_1 = 3.314 \times 0.026 = 0.083$ ) because the 95% CI did not include zero (0.014–0.163). This suggests that, on average, participants with Type D personality scored 0.083

points higher for HbA1c than those without due to the indirect effect via diabetes distress, when social isolation was kept constant. The indirect effect of Type D personality on HbA1c via social isolation was also statistically significant when controlling for diabetes distress ( $a_2 \times b_2 = 0.397 \times 0.136 = 0.054, 95\% \text{ CI} = 0.007 \text{ to } 0.121$ ). Comparing the magnitudes of the two indirect effects revealed an insignificant difference ( $95\% \text{ CI} = -0.061 \text{ to } 0.121$ ), and the total effect was also not statistically significant ( $c = 0.199, p = 0.096$ ).

### 3.3 | Hypothesis 2

Figure 2 (and Table S3) indicate that all regression coefficients were statistically significant, including the direct effect ( $c' = -0.326, p < 0.001$ ) of Type D personality on HRQOL when controlling for mediators and covariates. Table 2 indicates that there was a statistically significant indirect effect of Type D personality on HRQOL via diabetes distress when controlling for social isolation and covariates ( $a_1 \times b_1 = -0.254, 95\% \text{ CI} = -0.335 \text{ to } -0.178$ ). The indirect effect via social isolation was also statistically significant when controlling for diabetes distress and covariates ( $a_2 \times b_2 = -0.029, 95\% \text{ CI} = -0.056 \text{ to } -0.008$ ). The indirect effect via diabetes distress had a greater magnitude than that via social isolation ( $95\% \text{ CI} = -0.316 \text{ to } -0.145$ ), while the total effect was statistically significant ( $c = -0.609, p < 0.001$ ).

## 4 | DISCUSSIONS

### 4.1 | Findings for the study hypothesis

In this study, 31.3% of the participants with type 2 diabetes had Type D personality. This was consistent with the range of prevalence rates previously reported among Dutch (22.8–55.8%) (Nefs et al., 2015;

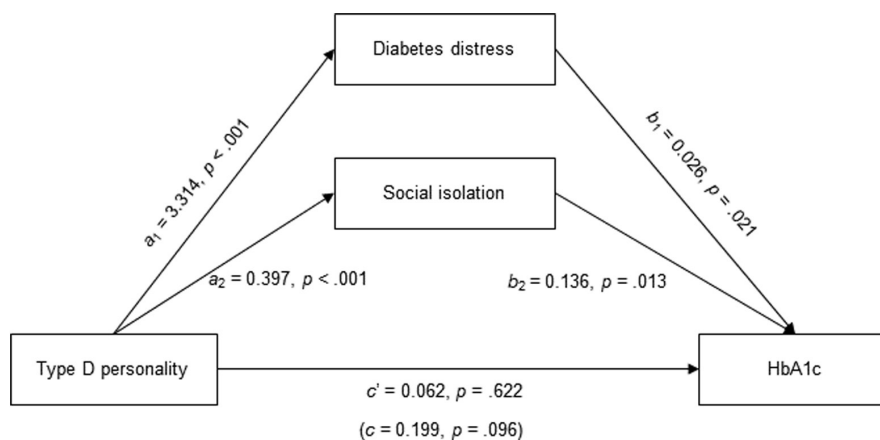
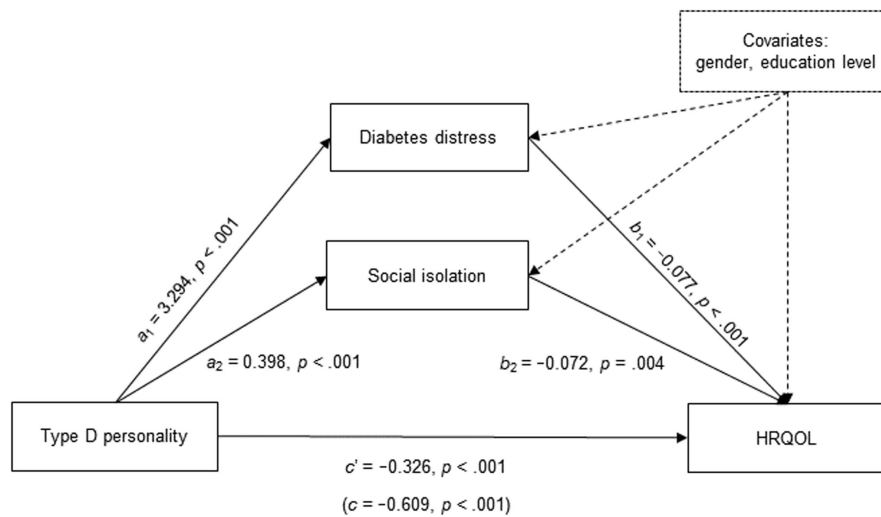


FIGURE 1 Parallel mediation model linking Type D personality with HbA1c. People with Type D personality were coded as 1 and others were coded as 0.  $a_1$ : Regression coefficient for Type D personality predicting diabetes distress;  $a_2$ : regression coefficient for Type D personality predicting social isolation;  $b_1$ : regression coefficient for diabetes distress predicting HbA1c while holding Type D personality and social isolation constant;  $b_2$ : regression coefficient for social isolation predicting HbA1c while holding Type D personality and diabetes distress constant;  $c'$ : regression coefficient for Type D personality predicting HbA1c while holding diabetes distress and social isolation constant (direct effect); and  $c$ : total effect.

**TABLE 1** Indirect effects on HbA1c with 95% bootstrap confidence interval

	Product of coefficient		95% bootstrap CI	
	Point estimate	Bootstrap SE	Lower limit	Upper limit
Indirect effects on HbA1c				
$a_1 \times b_1$	0.083	0.038	0.014	0.163
$a_2 \times b_2$	0.054	0.029	0.007	0.121
Comparison between indirect effects on HbA1c ( $a_1 \times b_1 - a_2 \times b_2$ )	0.029	0.046	-0.061	0.121

Abbreviations:  $a_1 \times b_1$ , indirect effect of Type D personality on HbA1c through diabetes distress;  $a_2 \times b_2$ , indirect effect of Type D personality on HbA1c through social isolation; CI, confidence interval; SE, standard error.



**FIGURE 2** Parallel mediation model linking Type D personality with HRQOL while controlling for covariates. People with Type D personality were coded as 1 and others were coded as 0.  $a_1$ : Regression coefficient for Type D personality predicting diabetes distress;  $a_2$ : regression coefficient for Type D personality predicting social isolation;  $b_1$ : regression coefficient for diabetes distress predicting HRQOL while holding Type D personality, social isolation, gender and education level constant;  $b_2$ : regression coefficient for social isolation predicting HRQOL while holding Type D personality, diabetes distress, gender and education level constant;  $c'$ : regression coefficient for Type D personality predicting HRQOL while holding diabetes distress, social isolation, gender and education level constant;  $c$ : total effect while controlling for gender and education level.

van Dooren et al., 2016) and Chinese (27.9–41.4%) (Li et al., 2016; Lin et al., 2020) adults with type 2 diabetes.

The mean HbA1c level of people with Type D personality did not differ from that of people without this personality, indicating that there was no direct association between Type D personality with HbA1c. Nefs et al. (2015) similarly reported no difference after subdividing people without Type D personality into three groups based on their scores relative to the cut-off of  $\geq 10$  for the NA and SI sum scores: NA<sup>+</sup>SI<sup>-</sup>, NA<sup>-</sup>SI<sup>+</sup> and NA<sup>-</sup>SI<sup>-</sup>. In contrast, another study analysing the continuous scores of the sums of NA and SI showed a statistically significant relationship between Type D personality and HbA1c (Conti et al., 2017).

Li et al. (2017) reported the controversial finding that the association between Type D personality and HbA1c appears to differ depending on whether Type D personality was considered a categorical or continuous variable. Type D personality is often measured as a

categorical variable (e.g. Type D vs. not Type D) with a criterion of  $\geq 10$  points. The cut-off score used in this categorical approach was criticized due to it being the median (Ferguson et al., 2009). However, the cut-off score was empirically demonstrated to accurately classify Type D versus not Type D using item response theory analysis among people with cardiovascular diseases (Emons et al., 2007). Those who have disagreed with the categorical approach insisted that Type D personality was more accurately represented by the continuous constructs of NA and SI (Ferguson et al., 2009), and was analysed more effectively using a continuous interaction method including quadratic NA and SI effects (Lodder, 2020). It seems to be important to reach a consensus on how to operationalize Type D personality.

The present study showed a statistically significant direct relationship between Type D personality and HRQOL. This finding is consistent with that of a previous study conducted on people with type

	Product of coefficient		95% bootstrap CI	
	Point estimate	Bootstrap SE	Lower limit	Upper limit
Indirect effects on HRQOL				
$a_1 \times b_1$	-0.245	0.040	-0.335	-0.178
$a_2 \times b_2$	-0.029	0.012	-0.056	-0.008
Comparison between indirect effects on HRQOL ( $a_1 \times b_1 - a_2 \times b_2$ )	-0.226	0.042	-0.312	-0.145

Abbreviations:  $a_1 \times b_1$ , indirect effect of Type D personality on HRQOL through diabetes distress;  $a_2 \times b_2$ , indirect effect of Type D personality on HRQOL through social isolation; CI, confidence interval; SE, standard error.

2 diabetes (Conti et al., 2017). That study measured HRQOL using a generic instrument (the World Health Organization QOL-BREF) that measures physical health, psychological variables (e.g. self-esteem), social relationships (e.g. social support) and environment (e.g. physical safety) (The WHOQOL Group, 1998). A generic instrument is applicable when measuring HRQOL on a healthy population or across healthy and diseased populations (Fayers & Machin, 2016), whereas a disease-specific HRQOL instrument designed to focus on specific problems induced by an illness such as diabetes and its treatment is more effective in clinical situations (Lee et al., 2012). It is therefore recommended that more studies are required into the relationship between Type D personality and HRQOL, with a particular focus on using a diabetes-specific HRQOL instrument.

The present study is the first to test hypotheses on the indirect effects of Type D personality on diabetes outcomes (HbA1c and HRQOL) via diabetes distress and social isolation, and these hypotheses were supported. This mediation-based research provided new information on how people with Type D personality readily experience negative emotions in response to the burden of living with diabetes, and how they might have fewer interpersonal contacts with others (e.g. family, friends or health professionals) and be more socially withdrawn, which will negatively impact blood glycaemic control and HRQOL. This new information may further the development of a comprehensive theory about Type D personality and its effects on people with type 2 diabetes.

#### 4.2 | Implications for practice and research

The findings of this study on the indirect effects suggest directions for furthering the clinical interventions applied to people with type 2 diabetes. It is recommended that nurses monitor clients with type 2 diabetes to determine whether Type D personality is present since this is a risk factor for adverse blood glycaemic control and HRQOL. These nurses must then plan and provide interventions aimed at reducing diabetes distress and social isolation, particularly among those with Type D personality. For example, providing diabetes-specific psychological interventions is recommended since a meta-analysis of randomized control trials showed that they reduce

TABLE 2 Indirect effects on HRQOL with 95% bootstrap confidence interval while controlling for covariates

diabetes distress (Schmidt et al., 2018). Others have indicated that using active listening and talking about the emotional experiences of patients also induce similar effects towards reducing diabetes distress when compared with a psychological intervention (Chew et al., 2018). Chen and Schulz (2016) asserted that social interventions based on information and communications technology (ICT) such as using the Internet or web-based apps would promote social contact and alleviate social isolation by providing connections with the outside world, improving social support, increasing engagement with activities of interest and boosting self-confidence. ICT interventions using digital devices may be particularly useful during the current coronavirus disease 2019 pandemic since this has increased experiences of no face-to-face contact, social distancing and restricted gatherings (Chatterjee & Yatnatti, 2020).

People with type D personality tend to have higher stress levels (Mols & Denollet, 2010b). A constant and poorly managed high stress level in people with type 2 diabetes will activate the dysregulation of hypothalamic-pituitary-adrenal (HPA) axis and release stress hormones (e.g. cortisol), while blood glucose levels may also worsen (Tsigos & Chrousos, 2002). Diabetes distress also has an adverse effect on glycaemic control via the dysregulation of stress hormones (Snoek et al., 2015). Based on the indirect effect of type D personality on HbA1c via diabetes distress found in this study, it is expected that there is an indirect relationship between the type D personality and HbA1c via diabetes distress and stress hormones serially; future studies should explore this relationship.

#### 4.3 | Strengths and limitation

The first strength of this study was the use of a bootstrapping method in the statistical mediation analysis. The traditional mediation test method introduced by Baron and Kenny (Baron & Kenny, 1986) has previously been the most common. However, that method has been criticized for its low statistical power and its lack of testing for indirect effects, and it no longer seems to be recommended (Lee et al., 2021; MacKinnon et al., 2002). The normal theory approach, called the Sobel test, has been used for mediation analysis but is criticized due to its inability to cope

with asymmetrically distributed indirect effects (MacKinnon et al., 2002). The bootstrapping method is recommended to overcome the requirement for a normality assumption, which gives more power in detecting indirect effects and reduces the risk of type I errors (Hayes & Scharkow, 2013). Structural equation modelling (SEM) is also frequently used for mediation analyses, and has the advantage of accounting for random measurement errors; however, the results obtained when analysing a sufficient sample can be substantially identical when applying the SEM and PROCESS methods (Hayes et al., 2017). The second strength of the present study was its consideration of potential covariates from among the general characteristics of the participants, which would have threatened the validity of the findings obtained when analysing the mediation model.

One limitation of the present study was its cross-sectional design, which induced difficult temporal interpretations of the mediation effects between Type D personality and adverse diabetes outcomes. A longitudinal design is recommended for further research.

## 5 | CONCLUSIONS

This study has revealed possible mechanisms underlying the relationships between Type D personality and adverse health outcomes (HbA1c and HRQOL) in people with type 2 diabetes. Type D personality was found to directly affect HRQOL but not HbA1c. Type D personality indirectly affected both HbA1c and HRQOL via the mediators of diabetes distress and social isolation. The indirect effect of Type D personality on HRQOL via diabetes distress had a greater magnitude than that via social isolation. We recommend providing interventions to people with Type D personality to reduce diabetes distress and alleviate social isolation, which in turn will improve their blood glucose control and HRQOL.

### AUTHOR CONTRIBUTIONS

E.-H.L.: study conception and design; funding acquisition; data analysis and interpretation; draft preparation, review and manuscript editing; and approval of the submitted version of the manuscript. Y.W.L., D.C., E.H.K. and H.-J.K.: investigation; data interpretation; review and editing of the manuscript; and approval of the submitted version of the manuscript.

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### CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

### DATA AVAILABILITY STATEMENT

The dataset used and/or analyzed during the current study are not publicly available due to ethical concerns.

### ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Research ethics committee approval was obtained from the institutional review boards of the included university hospitals in the Republic of Korea (approval numbers AJIRB-SBR-SUR-18-535, IUH-IRB 2020-05-036 and CNUH-2020-176). All participants gave their written informed consent.

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## SUPPORTING INFORMATION

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