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Loneliness, social isolation and incident chronic kidney disease among patients with diabetes

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ABSTRACT

Background Individuals with diabetes have a significantly higher risk of developing chronic kidney disease (CKD) and higher levels of social isolation and loneliness compared with those without diabetes. Recently, the American Heart Association highlighted the importance of considering social determinants of health (SDOH) in conjunction with traditional risk factors in patients with diabetes.

Aims To investigate the associations of loneliness and social isolation with incident CKD risk in patients with diabetes in the UK Biobank.

Methods A total of 18 972 patients with diabetes were included in this prospective study. Loneliness and Social Isolation Scales were created based on self-reported factors. An adjusted Cox proportional hazard model was used to investigate the associations of loneliness and social isolation with CKD risk among patients with diabetes. The relative importance in predicting CKD was also calculated alongside traditional risk factors.

Results During a median follow-up of 10.8 years, 1127 incident CKD cases were reported. A higher loneliness scale, but not social isolation, was significantly associated with a 25% higher risk of CKD, independent of traditional risk factors, among patients with diabetes. Among the individual loneliness factors, the sense of feeling lonely emerged as the primary contributing factor to the elevated risk of CKD. Compared with individuals not experiencing feelings of loneliness, those who felt lonely exhibited a 22% increased likelihood of developing CKD. In addition, feeling lonely demonstrated greater relative importance of predicting CKD compared with traditional risk factors such as body mass index, smoking, physical activity and diet.

Conclusions This study indicates the significant relationship between loneliness and CKD risk among patients with diabetes, highlighting the need to address SDOH in preventing CKD in this population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research has demonstrated significant associations between loneliness, social isolation and various health consequences, including cardiovascular diseases, dementia and other chronic diseases.

WHAT THIS STUDY ADDS

⇒ In this study, we investigated the prospective associations between loneliness, social isolation and the risk of chronic kidney disease (CKD) among adult participants with diagnosed diabetes from the UK Biobank cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study illuminates the critical link between loneliness and CKD risk in patients with diabetes, emphasising the need for holistic healthcare approaches that address both medical and psychosocial factors. Policymakers and healthcare providers should prioritise mental well-being assessments and interventions as vital components in diabetes management and CKD prevention strategies.

INTRODUCTION

Chronic kidney disease (CKD), a major public health concern, affects approximately 8%–16% of the global population.[1] As the primary cause of CKD, diabetes accounts for over 40% of CKD cases,[2] with individuals with diabetes being significantly more likely to develop CKD and end-stage renal disease compared with those without diabetes.[3]

The traditional risk factors for CKD in patients with diabetes, such as hyperglycaemia, hypertension, obesity, dyslipidaemia and smoking, have been well documented[4]; however, these factors do not fully capture the increased susceptibility to CKD in this population. Emerging research has suggested that additional factors, including environmental influences and psychosocial stressors, play a crucial role in the pathogenesis of CKD among patients with diabetes, pointing to the need for a broader exploration beyond traditional risk factors.[5]

The American Heart Association (AHA) has emphasised the significance of social determinants of (SDOH) in managing diabetes, advocating for a more holistic approach to patient care.[6] Within the SDOH framework, loneliness and social isolation have been identified as important elements influencing

health outcomes, each reflecting unique dimensions of social interaction.[7–9] Previous evidence suggests that loneliness and social isolation may influence health outcomes through several mechanisms. First, they may impact physiological processes, such as the stress response system and immune function, exacerbating inflammation and contributing to the progression of chronic conditions.[10] Second, loneliness may negatively affect health behaviours crucial for diabetes management, including physical activity levels and dietary choices, by diminishing motivation and increasing the likelihood of engaging in health-adverse behaviours.[11] Loneliness typically refers to the emotions associated with the quality of social connections, while isolation pertains to the number of social interactions in one's behaviour. The decision to focus on these factors over others within the SDOH spectrum is informed by growing evidence of their impact on health outcomes, particularly cardiovascular diseases (CVDs) and diabetes management.[7 8] Studies have shown that loneliness and social isolation not only exacerbate the risk factors associated with diabetes but also independently contribute to poor health outcomes, including CVD, dementia and potentially CKD.[12 13]

Previous research has established a significant link between loneliness, social isolation and increased CVD risk in patients with diabetes.[9] However, their associations with CKD risk, particularly in individuals with diabetes, remain largely unexplored. This gap in the literature presents an opportunity to investigate how these social factors, along with traditional risk factors, contribute to the development of CKD. In this study, we aimed to investigate the prospective associations between loneliness, social isolation and the risk of CKD among adult participants with diagnosed diabetes from the UK Biobank cohort. We particularly assessed the relative importance of loneliness and social isolation as opposed to traditional risk factors for predicting CKD risk.

METHODS

Study design and population

The UK Biobank study is a large population-based cohort, which enrolled over 500 000 participants representative of the general population. Participants were recruited at 22 assessment centres across the UK between 2006 and 2010. Comprehensive information about the UK Biobank's design and study population has been described previously.[14]

In the current study, our analysis focused solely on participants with diabetes at baseline, which was determined either by the onset time of diabetes (on or before the date of attending the assessment centre) or through a self-reported history of doctor-diagnosed diabetes (n=24 593) (online supplemental table S1). We identified a total of 18 972 patients with diabetes in our study after excluding 5552 participants with prevalent CKD and 69 participants with incomplete loneliness or isolation data (figure 1).

Loneliness and Isolation Scales

We developed the Scales of Loneliness and Social Isolation using baseline self-reported questionnaire according to previous UK Biobank studies.[15] First, the Loneliness Scale was evaluated by asking two questions: 'Do you often feel lonely?' (1 point for yes) and 'How often can you confide in someone close to you?' (1 point for no more than once a month). Second, the Social Isolation Scale was assessed by asking three questions: (1) 'Including yourself, how many people are living together in your household?' (1 point for living alone); (2) 'How often do you visit friends or family or have them visit you?' (1 point for having friends and family visit less than once a month); (3) 'Which of the following leisure/social activities do you engage in once a week or more often?' (1 point for not participating in social activity at least once per week). Those answers with low-risk factors were coded as 0. The sum of the responses to loneliness questions resulted in a scale ranging from 0 to 2 and social isolation questions in a scale ranging from 0 to 3. The detailed information on the scoring assessment for loneliness and social isolation can be found in online supplemental table S2.

Ascertainment of CKD

We defined CKD to encompass all stages (1–5) and used the International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes (N18, N18.1, N18.2,

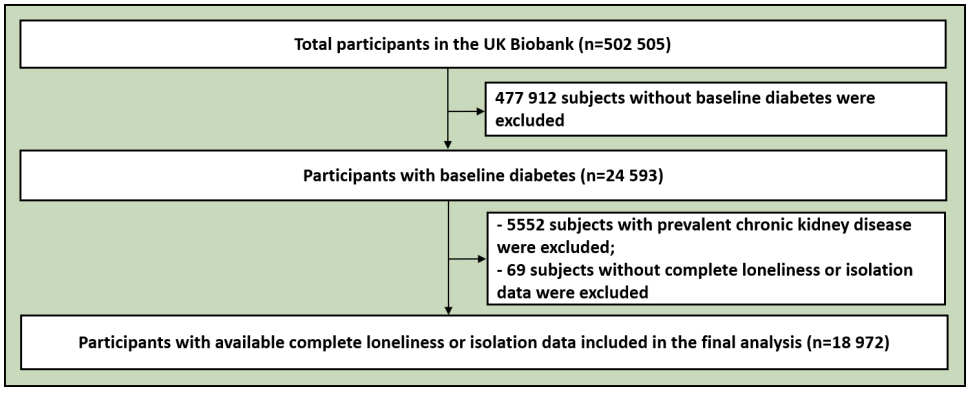

Figure 1 Flowchart of participants in the UK Biobank.

N18.3, N18.4, N18.5 and N18.9) to ascertain incident CKD cases.[16] Hospital inpatient records were obtained through linkages with the Hospital Episode Statistics for England, Scottish Morbidity Records for Scotland and Patient Episode Database for Wales. CKD-related deaths were identified by connecting to the death registry. The follow-up time in this study was calculated from the baseline date to the diagnosis of CKD, the censoring date or death (until May 2021), whichever occurred first. Detailed information on the ascertainment of outcomes is available online (https://biobank.ctsu.ox.ac.uk/showcase/label.cgi?id=2000).

To identify prevalent CKD, we used the ICD-10 codes mentioned before, or albuminuria above 3 mg/mmol, or the estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 at baseline.

Assessment of covariates

Self-reported information was collected by a touch-screen questionnaire, including age, sex, race, smoking status (never, past and current), alcohol consumption status (never, past and current) and medication use for cholesterol, blood pressure or diabetes. The Townsend deprivation index was gathered from local National Health Service Primary Care Trust registries and the name of the recruitment centre based on an individual's postcode, a composite measure of deprivation considering factors including unemployment, non-car ownership, non-home ownership and household overcrowding. A lower value represents a higher socioeconomic status. During the assessment visit, both height and weight were recorded, with body mass index (BMI) being determined by dividing the weight in kilograms by the square of height in metres (kg/m^2). eGFR was calculated by the CKD-EPI Creatinine Equation (2021) using the blood sample collected at baseline. Physical activity was measured by minutes of moderate or vigorous physical activity or an equivalent combination per week, and physical activity was defined according to the guideline as >150 min of moderate-intensity activity per week or >75 min of vigorous activity per week or an equivalent combination per week. Healthy diet scores were computed using a 0–5 scale, with 1 point assigned for each of these criteria: daily intake of fruits and vegetables, with at least 3 servings of each; weekly consumption of fish, with 2 or more servings; processed meat intake limited to less than 1 serving per week and unprocessed meat consumption restricted to 1.5 servings or fewer per week. Depressive symptoms were evaluated using two questions from the Patient Health Questionnaire-2, which addressed the frequency of depressed mood and disinterest or absence of enthusiasm in the previous 2 weeks. Participants' responses of 'not at all', 'several days', 'more than half the days' or 'nearly every day' were assigned scores of 0, 1, 2 and 3, respectively. By summing the scores for both items, the overall Depression Score was determined, ranging from 0 to 6. Diabetes duration was defined via the health records. We assigned a missing indicator category for categorical variables with missing covariates, and we used mean values for continuous variables with missing data. More in-depth information on these measurements can be found on the UK Biobank's website (https://biobank.ctsu.ox.ac.uk/showcase).

Statistical analysis

Continuous variables are presented as mean (SD) while categorical variables are expressed as counts with percentages according to the Scale of Loneliness and Social Isolation. Statistical significance was determined using χ^2 tests for categorical variables and general linear models after adjusting for age (except age) for continuous variables. Cox proportional hazards models were employed to assess the association between the Loneliness Scale or Isolation Scale or individual loneliness factors or individual isolation factors and the risk of CKD separately, with follow-up years serving as the underlying time metric. The proportional hazards assumption was evaluated using Schoenfeld residuals, and all analyses met the required criteria. Confounders were selected based on the association with outcome and exposure, as well as the review of literature.[9] We adjusted several potential confounders in these models. Model 1 was adjusted for basic demographic and socioeconomic factors: age, sex, race and Townsend deprivation index. Model 2 was built on Model 1 by further adjusting for lifestyle factors, including physical activity, healthy diet score, smoking status, alcohol use and BMI. Model 3, based on Model 2, included additional adjustments for medical and psychological factors: eGFR, diabetes duration, the use of diabetes medication, cholesterol-lowering medication, antihypertensive medication and depression score. This model aimed to provide a comprehensive adjustment for medical and psychological factors that could further confound the relationship between our variables of interest and CKD risk. By progressively adjusting for different types of variables, we aimed to disentangle the complex interplay of demographic, lifestyle, medical and psychological factors influencing CKD risk in patients with diabetes. To assess the importance of loneliness or isolation in predicting CKD, we analysed the relative importance of loneliness or isolation alongside some traditional risk factors by calculating the R^2 values of the Cox models,[17] and we tested the results' consistency by calculating the explainable log-likelihood that was attributable to each risk factor.

Furthermore, we performed stratified analyses by sex (women or men), race (white or non-white), Townsend deprivation index (quintiles 1, quintiles 2–4, quintiles 5), obesity (no or yes), smoking status (current or non-current smoker), alcohol use (current or non-current drinker), eGFR (<90 or ≥90 mL/min/1.73 m^2), healthy diet score (<median or ≥median), depression score (<3 or ≥3), regular physical activity (no or yes), duration of diabetes (<5, 5–10 and ≥10 years), antihypertensive drug use (no or yes), diabetes drug use (no or yes) and cholesterol-lowering drug use (no or yes). To assess interactions between the Loneliness Scale and these factors,

Table 1 Baseline characteristics of participants with diabetes by loneliness score

Characteristics	Loneliness score				
	0	1	2	Statistic*	P value*†
Number of participants, n (%)	11 738 (61.9)	5523 (29.1)	1711 (9.0)		
Age, years	59.8 (7.0)	59.3 (7.1)	57.9 (7.2)	99.7	<0.001
Female sex, n (%)	4324 (36.8)	2107 (38.2)	659 (38.5)	3.8	0.150
White ethnicity, n (%)	10 471 (89.2)	4693 (85.0)	1509 (88.2)	63.4	<0.001
Townsend deprivation index	–0.9 (3.2)	–0.1 (3.5)	0.4 (3.6)	308.8	<0.001
BMI, kg/m^2	30.7 (5.4)	31.3 (5.8)	32.2 (6.1)	92.3	<0.001
Diabetes duration, years	8.3 (10.3)	8.5 (10.5)	8.5 (10.2)	2.2	0.141
Current smoker, n (%)	1055 (9.0)	687 (12.4)	672 (39.3)	102.9	<0.001
Current drinker, n (%)	10 151 (86.5)	4579 (82.9)	1390 (81.2)	55.0	<0.001
Physical active, n (%)‡	6340 (54.0)	2645 (47.9)	765 (44.7)	89.9	<0.001
Healthy diet score	2.7 (1.3)	2.6 (1.3)	2.4 (1.3)	92.5	<0.001
Depression score	0.4 (1.0)	1.1 (1.5)	2.2 (1.8)	2969.3	<0.001
eGFR, mL/min/1.73 m^2	93.7 (13.6)	93.1 (13.9)	93.2 (14.0)	54.4	<0.001
Antihypertensive medication, n (%)	7065 (60.2)	3344 (60.5)	1015 (59.3)	0.7	0.698
Cholesterol-lowering medication, n (%)	8778 (74.8)	4060 (73.5)	1265 (73.9)	9.8	0.016
Diabetes medication, n (%)	8158 (69.5)	3945 (71.4)	1246 (72.8)	12.2	0.002

Values are means (SD) for continuous variables and n (%) for categorical variables.
*F values for continuous variables and χ^2 values for categorical values.
†P values were calculated by χ^2 test for categorical variables and general linear models for continuous variables after adjusting for age (except age) for baseline characteristics.
‡Physical activity was calculated as minutes of moderate or vigorous physical activity or an equivalent combination per week; according to the guideline, being physically active was defined as engaging in >150 min of moderate-intensity activity weekly, >75 min of vigorous-intensity activity or a comparable mix of the two.
BMI, Body Mass Index; eGFR, estimated glomerular filtration rate.

multiplicative interaction was evaluated by adding interaction terms to the original Cox models. In the sensitivity analyses, we additionally adjusted for feeling lonely and confiding in someone close mutually in the model. And we further adjusted for Social Isolation Scale in this model to assess the association between individual loneliness factors and the risk of CKD among patients with diabetes at baseline.

All statistical analyses were conducted using SAS V.9.4 TS Level 1M7 (SAS Institute) and R V.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-tail p value less than 0.05 was considered statistically significant.

RESULTS

Study population

The baseline information for patients with diabetes without pre-existing CKD, categorised by the Loneliness Scale or Social Isolation Scale is displayed in table 1 and online supplemental table S3. Of the 18 972 patients with diabetes, 61.9% had a loneliness score of 0, 29.1% scored 1 and 9.0% had a score of 2 (table 1). For participants with a social isolation score of 0, 1, 2 or 3, the respective percentages were 45.5%, 41.7%, 11.6% and 1.2% (online supplemental table S3). Individuals with lower scores on the Loneliness or Social Isolation Scales were generally older, less likely to be white, exhibited a lower Townsend deprivation index and were more likely to be non-smokers, current drinkers and maintain a healthy diet compared with those with higher scores on these scales. Furthermore, patients with lower loneliness or social isolation scores demonstrated a tendency towards lower BMI, depression scores and higher eGFR and reduced likelihood of insulin and cholesterol-lowering medication use (all p<0.05).

Association of loneliness or social isolation with CKD risk in patients with diabetes

During a median follow-up of 10.8 years, a total of 1127 incidents with CKD events were observed among patients with diabetes at baseline. Our results indicated that the Loneliness Scale, rather than the Isolation Scale, had a significant association with an increased risk of CKD in patients with diabetes (table 2). In the sex, age, race and Townsend deprivation index adjusted model, a Higher Loneliness Scale was significantly associated with a higher risk of CKD, with hazard ratios (HRs) (95% CI) of 0 (reference), 1.21 (1.06 to 1.38) and 1.42 (1.17 to 1.73) across the Loneliness Scales of 0, 1 and 2 (P-trend <0.001). After further adjustment for physical activity, healthy diet score, smoking, alcohol use, BMI, the association was slightly attenuated but still significant with HRs

Table 2 Multivariable-adjusted HRs (95% CIs) of Loneliness and Social Isolation Scales for chronic kidney disease among patients with diabetes at baseline

	Chronic kidney disease			
	Cases (n)/total	Model 1	Model 2	Model 3
Loneliness Scale				
0	647/11 738	1 (Reference)	1 (Reference)	1 (Reference)
1	360/5523	1.21 (1.06 to 1.38)	1.16 (1.02 to 1.33)	1.11 (0.95 to 1.28)
2	120/1711	1.42 (1.17 to 1.73)	1.34 (1.09 to 1.63)	1.25 (1.00 to 1.57)
P-trend		<0.001	<0.001	0.019
Social Isolation Scale				
0	472/8631	1 (Reference)	1 (Reference)	1 (Reference)
1	488/7914	1.14 (1.08 to 1.18)	1.03 (0.97 to 1.26)	1.01 (0.88 to 1.17)
2	151/2193	1.32 (1.09 to 1.59)	1.27 (1.05 to 1.53)	1.14 (0.92 to 1.40)
3	16/234	1.35 (0.82 to 2.23)	1.22 (0.73 to 2.05)	1.14 (0.65 to 1.99)
P-trend		0.002	0.013	0.115

Model 1 was adjusted for sex, age, race and Townsend deprivation index.
Model 2: Model 1+physical activity, healthy diet score, smoking, alcohol use and body mass index.
Model 3: Model 2+estimated glomerular filtration rate, diabetes duration, the use of diabetes medication, cholesterol-lowering medication, antihypertensive medication and depression score.

(95% CI) of 1.16 (1.02 to 1.33) and 1.34 (1.09 to 1.63) for participants with a Loneliness Scale of 1 and 2 (p-trend <0.001). The observed association showed a modest attenuation if we further included eGFR, diabetes duration, the use of diabetes medication, cholesterol-lowering medication, antihypertensive medication and depression score into the model with HRs (95% CI) of 1.11 (0.95 to 1.28) and 1.25 (1.00 to 1.57) for participants with a Loneliness Scale of 1 and 2 (P-trend=0.019) (table 2). In addition, the associations between individual loneliness or social isolation factors and the risk of CKD are shown in table 3 and online supplemental table S4. Regarding the individual loneliness factors, we found that the feeling-lonely aspect, rather than confiding in someone close, was significantly associated with an increased CKD risk. In the multivariable-adjusted model, when comparing participants without feeling lonely, those who felt lonely exhibited an HR (95% CI) of 1.22 (1.04 to 1.43) for CKD risk (table 3). In the sensitivity analyses, similar associations were observed when we adjusted for feeling lonely and confiding in someone close mutually in the model. The results were not changed when we further adjusted Social Isolation Scale in this model (online supplemental table S5). However, regarding the individual social isolation factors, we did not observe a significant association between any individual factors of social isolation and the risk of CKD (online supplemental table S4).

Furthermore, we conducted stratified analyses according to potential risk factors (online supplemental table S6) to evaluate whether these covariables modified the relationship between the Loneliness Scale and the risk of CKD. However, we did not find significant interactions

Table 3 Multivariable-adjusted HRs (95% CIs) of individual loneliness factors for chronic kidney disease among patients with diabetes at baseline

	Chronic kidney disease			
Loneliness factors	Cases (n)/total	Model 1	Model 2	Model 3
Feeling lonely				
0	813/14 254	1 (Reference)	1 (Reference)	1 (Reference)
1	299/4361	1.32 (1.15 to 1.51)	1.25 (1.09 to 1.44)	1.22 (1.04 to 1.43)
Confiding in someone close				
0	783/13 636	1 (Reference)	1 (Reference)	1 (Reference)
1	301/4584	1.16 (1.01 to 1.32)	1.13 (0.99 to 1.29)	1.06 (0.91 to 1.24)

Model 1 was adjusted for sex, age, race and Townsend deprivation index.
Model 2: Model 1+physical activity, healthy diet score, smoking, alcohol use and body mass index.
Model 3: Model 2+estimated glomerular filtration rate, diabetes duration, the use of diabetes medication, cholesterol-lowering medication, antihypertensive medication and depression score.

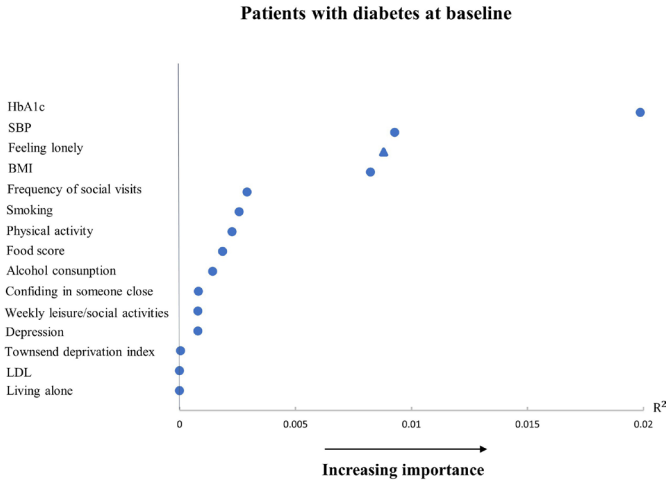

Figure 2 Relative importance of factors for predicting incident chronic kidney disease (CKD) among patients with diabetes at baseline. The estimated explained relative risk (ie, relative importance) shows the strength of the association for various variables for predicting CKD incidence among patients with diabetes. The analysis was restricted to patients with diabetes. We constructed a Cox hazard model for the outcome, which included every predictor. R^2 was generated by developed applications for the Cox model and is bounded between 0 and 1. Risk factors showing a clear and substantial R^2 measure, as compared with other adjacent predictors, are relevant. The model included two individual loneliness factors, Social Isolation Scale, sex, age, race, Townsend deprivation index, physical activity, healthy diet score, smoking, alcohol use, BMI, estimated glomerular filtration rate, albumin-to-creatinine ratio, diabetes duration, the use of diabetes medication, cholesterol-lowering medication, antihypertensive medication, depression score, SBP, HbA1c and LDL-cholesterol. BMI, body mass index; LDL, low-density lipoprotein; SBP, systolic blood pressure.

between these covariates and the Scale of Loneliness on the risk of CKD.

The relative importance of loneliness and social isolation factors compared with traditional risk factors in predicting CKD events among patients with diabetes

We evaluated the relative importance of each loneliness factor and social isolation factor in predicting CKD incidence among patients with diabetes in comparison to other traditional risk factors (figure 2). In our investigation of specific loneliness factors, we found that feeling lonely held the 3rd position in relation to CKD risk among individuals with diabetes, while the other factor of loneliness (confiding in someone else) was the 10th position. The predictive capacity of feeling lonely for CKD was surpassed by HbA1c and systolic blood pressure. Nevertheless, feeling lonely ranked higher than several traditional risk factors including BMI, smoking, physical activity, alcohol, dietary scores and depression scores, Townsend deprivation index and low-density lipoprotein-cholesterol in predicting CKD. As for the exploration of particular social isolation elements, the frequency of social visits ranked 5th, though the association was not significant. The remaining two factors ranked even lower, specifically 11th and 15th, with non-significant associations. The results with the use of explained log-likelihood were consistent with the results obtained using the explained relative risk (R^2) models (online supplemental figure S1).

DISCUSSION

Main findings

In this large prospective cohort, the associations of loneliness and social isolation with the risk of incident CKD were investigated in individuals with diabetes. We observed that a higher loneliness scale, but not social isolation, was significantly associated with a 25% higher risk of CKD among patients with diabetes. Among the individual loneliness factors, the sense of feeling lonely, as opposed to having someone to confide in, emerged as the primary factor contributing to the elevated risk of CKD. Compared with individuals who did not feel lonely, those experiencing feelings of loneliness demonstrated a 22% higher probability of CKD development. In our analysis, we observed a sequential decrease in the effect sizes from Model 1 to Model 3. This trend can be attributed to the progressive inclusion of various confounding factors across the models. As we adjusted for more variables that could independently affect CKD risk, the isolated impact of loneliness factors became more refined and potentially more representative of their true effect. In addition, feeling lonely demonstrated greater relative importance in predicting CKD compared with traditional risk factors such as BMI, smoking, physical activity and diet.

Our study, for the first time, showed that loneliness was significantly related to a higher risk of CKD in patients with diabetes. Our findings are partly supported by previous studies which have primarily focused on the relationship between loneliness and cardiovascular health. For instance, studies in the general population have demonstrated that loneliness is associated with higher risks of CVD events.[9 18] We recently demonstrated a significant association between the Loneliness Scale and increased risks of total CVD and coronary heart disease among individuals with diabetes, as evidenced by higher HRs of 1.15 (95% CI 1.07 to 1.25) and 1.38 (95% CI 1.23 to 1.54) for participants with loneliness scores of 1 and 2, respectively, compared with those with the lowest loneliness score (0).[9] Moreover, in an English longitudinal study, loneliness has been linked to an increased risk of developing both coronary heart disease and stroke, irrespective of traditional risk factors associated with CVDs.[18] Another cohort study among older women from the USA revealed that a high loneliness score corresponded to a 14% increase in the hazard of CVD compared with a low loneliness score. The mechanisms linking loneliness to CVD, such as dysregulation of the autonomic nervous system and increased systemic inflammation, are also pertinent in the context of CKD.[19] This overlap in pathophysiological pathways suggests that factors influencing CVD might similarly

impact CKD, especially in patients with diabetes where vascular health is already compromised.

Given the established relationship between loneliness and CVD, it's crucial to explore how these psychosocial stressors extend their influence on CKD. Both CVD and CKD are vascular complications often observed in diabetes, sharing common risk factors such as hypertension and poor glycaemic control. Our investigation into the impact of loneliness on CKD stems from this interconnection, hypothesising that the psychosocial stressors contributing to CVD might similarly influence CKD progression. In this study, we recognised the dual role of loneliness in CKD risk among patients with diabetes. As a confounder, loneliness, independently linked with both diabetes and CKD, emerges as a significant risk factor for type 2 diabetes.[20] This emphasises its importance in CKD risk analysis. Additionally, loneliness might also act as an effect mediator: diabetes-related factors like reduced mobility can increase loneliness, which in turn may exacerbate CKD progression.[21] In addition, we investigated the associations between different aspects of loneliness (ie, feeling lonely and the frequency of confiding in someone close) and the risk of CKD among patients with diabetes. Intriguingly, the subjective experience of feeling lonely, but not the frequency of confiding in someone close, showed a significant association with the risk of CKD. The subjective experience of feeling lonely encompasses emotional and cognitive aspects, reflecting an individual's perception of social isolation and a lack of connection with others.[22] Moreover, we compared the relative importance of each aspect of loneliness with traditional risk factors in predicting CKD among patients with diabetes. We found that the relative strength of feeling lonely was greater than several traditional risk factors such as BMI, smoking, physical activity and diet, highlighting the importance of considering psychosocial factors in preventing CKD complications in patients with diabetes, beyond traditional risk factors. Our findings support the recent statement by the AHA that SDOH is important among patients with diabetes in preventing vascular complications.

Incorporating psychosocial factors into the prevention of vascular complications in patients with diabetes offers several potential benefits. First, unlike traditional risk factors that predominantly affect the biological aspect, psychosocial factors can impact health behaviours and self-care practices.[23] Feeling lonely may lead to decreased motivation and poor adherence to diabetes management strategies. Second, psychosocial factors have been linked to cardiovascular health.[13 18] Loneliness and other psychosocial stressors have been associated with dysregulation of the autonomic nervous system and the hypothalamic–pituitary–adrenal axis, impaired immune functioning[24] and increased systemic inflammation. These mechanisms, in conjunction with traditional risk factors, can contribute to the development and progression of vascular complications, such as CKD, in patients with diabetes. Even though the precise mechanisms between loneliness and CKD remain unclear, several other potential explanations are worthy of consideration. Loneliness is related to impaired self-regulation, such as physical inactivity, alcohol abuse, sleep disturbances and physiological changes in cardiovascular health, such as elevated blood pressure.[25] All these mechanisms may play a role in the development of CKD in patients with diabetes. Therefore, while traditional risk factors remain critical, the multifaceted impact of loneliness highlights its unique and potent role in CKD development. Recognising this, it becomes imperative to incorporate psychosocial health management as part of comprehensive CKD prevention strategies in diabetic care.

We did not find a significant association between social isolation and CKD among patients with diabetes. This finding diverges from several studies investigating social isolation/support and kidney health outcomes.[26 27] For example, a nationally representative longitudinal survey, China Health and Retirement Longitudinal Study, reported a significant association between social isolation and increased risks of rapid eGFR decline and CKD onset in middle-aged and older adults with normal kidney function in mainland China.[26] Additionally, an update about social support and CKD mentioned that social support emerges as an important modifiable risk factor across chronic diseases, including end-stage renal disease.[27] One possible explanation for this discrepancy is that patients with diabetes may have distinct social support needs or coping mechanisms compared with the broader population, thereby attenuating the impact of social isolation on CKD risk. Alternatively, the measures used to assess social isolation in our study may not have fully captured the complexity of this construct in relation to CKD risk among patients with diabetes. However, our results align with several prior investigations. For example, a systematic review and meta-analysis found no significant link between low structural social support and the prevalence of myocardial infarction in healthy populations.[28] In addition, our findings are also in line with our recent findings that social isolation is not related to CVDs among individuals with diabetes.[9] Loneliness and social isolation, though inter-related, are separate notions. Loneliness embodies the subjective sense of solitude, disconnection or absence of companionship, often arising from a perceived deficiency in one's social connections. In contrast, social isolation denotes an objective condition characterised by a limited number of social ties, a constrained social network or sporadic social engagement. Loneliness is an emotional state, while social isolation can be quantified as a facet of an individual's social existence.[29] Notably, a person may experience feeling lonely without social isolation. Our results indicated that the qualitative aspects of the social environment (emotional) might hold greater significance than the quantitative dimensions (behavioural) when assessing the risk of CKD among individuals with diabetes. The major strengths include its prospective design, the sizeable cohort of patients with diabetes with available data on loneliness and isolation,

and the extensive, detailed information on covariates in this population.

Limitations

However, we recognise several potential limitations. First, the loneliness and social isolation measures were based on simple questions, which may not fully capture the complexities of social construction and interaction. Nonetheless, these measures have been employed in numerous prior studies, implying their effectiveness in population research.[18] Second, generalisability is another limitation, as over 90% of the UK Biobank cohort is composed of people of white ancestry. Further investigations are needed for other racial/ethnic groups. Third, UK Biobank participants are more likely to exhibit healthier behaviours compared with the overall UK population. However, this would not compromise the internal validity of this study. Fourth, as an observational study, we cannot infer causality between loneliness and CKD risk. Fifth, our analysis might not fully capture the complex interplay between the specific biological mechanisms of type 1 and type 2 diabetes, and how these distinct mechanisms might differentially interact with psychosocial factors. Their subsequent influence on CKD risk represents an area that warrants further, more detailed investigation. Finally, despite accounting for several potential confounders, the possibility of residual confounding cannot be entirely excluded.

Implications

Our findings indicate that a higher loneliness scale, rather than social isolation, is significantly associated with a higher CKD risk among individuals with diabetes. Furthermore, the sensation of feeling lonely exhibited higher relative strength in predicting CKD in comparison to traditional risk factors such as BMI, smoking, physical activity and diet, highlighting the importance of considering psychosocial factors in preventing vascular complications in patients with diabetes.

Contributors LQ had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Planning: LQ and RT. Conduct: RT and JZ. Reporting: RT, JZ and XW. Concept and design: LQ and RT. Acquisition of data: LQ, RT and HM. Analysis of data: RT and JZ. Interpretation of data: LQ, RT and XL. Critical revision of the manuscript for important intellectual content: LQ, RT, JZ, XW, HM, XL and YH. Drafting of the manuscript: LQ and RT. Statistical analysis: RT. Overall content guarantors: LQ and RT.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The study received approval from the Northwest Multi-Centre Research Ethics Committee (11/NW/0382) and the Tulane University (New Orleans, Louisiana, USA) Biomedical Committee Institutional Review Board (2018-1872). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. This study has been conducted using the UK Biobank Resource, approved project number 29256. The UK Biobank will make the source data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any persons. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website (http://www.ukbiobank.ac.uk/register-apply).

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REFERENCES

1 Jha V, Garcia-Garcia G, Iseki K, *et al*. Chronic kidney disease: global dimension and perspectives. *The Lancet* 2013;382:260–72.
2 Bailey RA, Wang Y, Zhu V, *et al*. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on kidney disease: improving global outcomes (KDIGO) staging. *BMC Res Notes* 2014;7:415.
3 New JP, Middleton RJ, Klebe B, *et al*. Assessing the prevalence, monitoring and management of chronic kidney disease in patients with diabetes compared with those without diabetes in general practice. *Diabet Med* 2007;24:364–9.
4 Kazancioğlu R. Risk factors for chronic kidney disease: an update. *Kidney Int Suppl (2011)* 2013;3:368–71.
5 Bruce MA, Beech BM, Sims M, *et al*. Social environmental stressors, psychological factors, and kidney disease. *J Investig Med* 2009;57:583–9.
6 Joseph JJ, Deedwania P, Acharya T, *et al*. Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: a scientific statement from the American Heart Association. *Circulation* 2022;145:e722–59.
7 Hill-Briggs F, Adler NE, Berkowitz SA, *et al*. Social determinants of health and diabetes: a scientific review. *Diabetes Care* 2020;44:258–79.
8 Powell-Wiley TM, Baumer Y, Baah FO, *et al*. Social determinants of cardiovascular disease. *Circ Res* 2022;130:782–99.
9 Wang X, Ma H, Li X, *et al*. Joint association of loneliness and traditional risk factor control and incident cardiovascular disease in diabetes patients. *Eur HEART J* 2023;44:2583–91.
10 Jaremka LM, Fagundes CP, Peng J, *et al*. Loneliness promotes inflammation during acute stress. *Psychol Sci* 2013;24:1089–97.
11 Kobayashi LC, Steptoe A. Social isolation, loneliness, and health behaviors at older ages: longitudinal cohort study. *Ann Behav Med* 2018;52:582–93.
12 Salinas J, Beiser AS, Samra JK, *et al*. Association of loneliness with 10-year dementia risk and early markers of vulnerability for neurocognitive decline. *Neurology* 2022;98:e1337–48.
13 Smith RW, Barnes I, Green J, *et al*. Social isolation and risk of heart disease and stroke: analysis of two large UK prospective studies. *Lancet Public Health* 2021;6:e232–9.
14 Sudlow C, Gallacher J, Allen N, *et al*. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLOS Med* 2015;12:e1001779.
15 Elovainio M, Hakulinen C, Pulkki-Råback L, *et al*. Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK biobank cohort study. *Lancet Public Health* 2017;2:e260–6.
16 Roy L, Zappitelli M, White-Guay B, *et al*. Agreement between administrative database and medical chart review for the prediction

of chronic kidney disease G category. *Can J Kidney Health Dis* 2020;7:2054358120959908.
17 Rawshani A, Rawshani A, Franzén S, *et al*. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2018;379:633–44.
18 Valtorta NK, Kanaan M, Gilbody S, *et al*. Loneliness, social isolation and risk of cardiovascular disease in the English longitudinal study of ageing. *Eur J Prev Cardiol* 2018;25:1387–96.
19 Cachofeiro V, Goicochea M, De Vinuesa SG, *et al*. Oxidative stress and inflammation, a link between chronic kidney disease and cardiovascular disease: new strategies to prevent cardiovascular risk in chronic kidney disease. *Kidney Int* 2008;74:S4–4S9.
20 Henriksen RE, Nilsen RM, Strandberg RB. Loneliness increases the risk of type 2 diabetes: a 20 year follow-up–results from the HUNT study. *Diabetologia* 2023;66:82–92.
21 Kobos E, Szewczyk A, Kokoszka-Paszkot J, *et al*. Factors associated with loneliness in patients with diabetes mellitus. *Nurs Open* 2021;8:517–24.
22 Perlman D. *Toward a social psychology of loneliness in personal relationships in disorder*. 1981.
23 Lerman I, Lozano L, Villa AR, *et al*. Psychosocial factors associated with poor diabetes self-care management in a specialized center in Mexico city. *Biomed Pharmacother* 2004;58:566–70.
24 Steptoe A, Owen N, Kunz-Ebrecht SR, *et al*. Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. *Psychoneuroendocrinology* 2004;29:593–611.
25 Cacioppo JT, Hawkley LC, Crawford LE, *et al*. Loneliness and health: potential mechanisms. *Psychosom Med* 2002;64:407–17.
26 Zhou W, Li Y, Ning Y, *et al*. Social isolation is associated with rapid kidney function decline and the development of chronic kidney diseases in middle-aged and elderly adults: findings from the China health and retirement longitudinal study (CHARLS). *Front Med (Lausanne)* 2021;8:782624.
27 Cohen SD, Sharma T, Acquaviva K, *et al*. Social support and chronic kidney disease: an update. *Adv Chronic Kidney Dis* 2007;14:335–44.
28 Barth J, Schneider S, von Känel R. Lack of social support in the etiology and the prognosis of coronary heart disease: a systematic review and meta-analysis. *Psychosom Med* 2010;72:229–38.
29 De Jong Gierveld J. Loneliness and social isolation. In: Perlman DVangelisti A, eds. *The Cambridge handbook of personal relationships*. 2006: 485–500.

Rui Tang will graduate with a PhD in May 2024 from the Epidemiology Department at Tulane University's School of Public Health and Tropical Medicine, where she has been advancing her research since 2020. Rui has been honoured with the Epidemiology Department Scholarship, Delta Omega National Honorary Society in Public Health and Dorothy LeBlanc Memorial Scholarship Award. She obtained her master's degree in Public Health from Tulane, the USA in 2019 with the Dean's Outstanding Student Award. Rui holds an MSc in Food Security from the University of Warwick (2016) in the UK and received her bachelor's degree from the Ocean University of China (2011–2015). Her seminal research contributions, particularly concerning diet, gut microbiota and their links to diseases such as type 2 diabetes and chronic kidney disease, have garnered attention at premier conferences, including the American Heart Association and American Diabetes Association. She has first- author publications in the American Journal of Clinical Nutrition, JAMA Network Open and American Journal of Kidney Disease. Additionally, she has co-authored articles in Diabetes, Obesity & Metabolism, the American Journal of Obstetrics and Gynecology, BMC Medicine and Mayo Clinic Proceedings. As she spearheads innovative epidemiological studies, Rui remains committed to enhancing public health understanding globally.

Loneliness, social isolation and incident chronic kidney disease among diabetes patients

Supplementary Materials

Table of Content

Table S1. Definitions of prevalent diabetes.

	Source and definition
Diabetes at baseline: both possible (including type 1, type 2 and other types of diabetes) and probable (including type 1, type 2 and other types of diabetes) diabetes at baseline	Self-reported at baseline[1]; Medication for diabetes at baseline[1]; International Classification of Diseases, Ninth Revision (ICD-9): 250, 6480 (if incident time ≤ Date of attending assessment centre); International Classification of Diseases, Tenth Revision (ICD10): E10, E11, E12, E13, E14, O24 (if incident time ≤ Date of attending assessment centre).

1. Eastwood SV, Mathur R, Atkinson M, et al. Algorithms for the capture and adjudication of prevalent and incident diabetes in UK Biobank. PLoS One. 2016. 11(9): e0162388.

Table S2. Assessment of social isolation and loneliness in the UK Biobank

Indicators	UK Biobank field ID	Touchscreen questions	Responses	Score
Social isolation indicators	709	Including yourself, how many people are living together in your household?	Not living alone. Living alone	0 1
	1031	How often do you visit friends or family or have them visit you?	Almost daily 2–4 times a week About once a week About once a month Once every few months Never or almost never No friends/family outside household	0 1
	6160	Which of the following (sports club or gym, pub or social club, religious group, adult education class, other group activity) do you attend once a week or more often?	Sports club or gym Pub or social club Religious group Adult education class Other group activity None of the above	0 1
Loneliness indicators	2020	Do you often feel lonely?	No Yes	0 1
	2110	How often are you able to confide in someone close to you?	Almost daily 2–4 times a week About once a week About once a month Once every few months Never or almost never	0 1

Table S3. Baseline characteristics of participants with diabetes by social isolation score.

Characteristics	Social isolation score			
	0	1	2	3
No. of participants	8631 (45.5)	7914 (41.7)	2193 (11.6)	234 (1.2)
Age, years	59.9 (7.0)	59.4 (7.1)	58.6 (7.2)	58.2 (6.9)
Female sex, n (%)	3053 (35.4)	3144 (39.7)	827 (37.7)	66 (28.2)
White ethnicity, n (%)	7560 (87.6)	6989 (88.3)	1920 (87.6)	204 (87.2)
Townsend deprivation index	−1.1 (3.1)	−0.3 (3.4)	0.7 (3.6)	2.2 (3.4)
Body mass index, kg/m^2	30.7 (5.5)	31.3 (5.9)	31.6 (6.0)	32.3 (6.8)
Diabetes duration, years	8.4 (10.4)	8.3 (10.2)	8.4 (10.6)	9.2 (10.9)
Current smoker, n (%)	676 (7.9)	892 (11.3)	391 (18.0)	55 (23.5)
Current drinker, n (%)	7536 (87.5)	6659 (84.3)	1752 (80.0)	173 (74.6)
Physical activity, n (%)[a]	4995 (57.9)	3750 (47.4)	931 (42.5)	74 (31.6)
Healthy diet score	2.7 (1.2)	2.6 (1.3)	2.5 (1.3)	2.4 (1.3)
Depression score	0.6 (1.4)	0.8 (1.4)	1.2 (1.6)	1.7 (2.0)
eGFR, mL/min/1.73 m^2	93.9 (13.6)	93.3 (13.6)	92.6 (14.3)	92.1 (14.0)
Antihypertensive medication, n (%)	5202 (61.3)	4717 (60.6)	1357 (63.1)	148 (64.4)
Cholesterol-lowering medication, n (%)	6465 (76.2)	5842 (75.0)	1620 (75.4)	176 (76.5)
Diabetes medication, n (%)	5970 (69.2)	5600 (70.8)	1601 (73.0)	178 (76.1)

Values are means (SD) for continuous variables and n (%) for categorical variables.
BMI=body mass index; eGFR= estimated glomerular filtration rate.
[a], physical activity was calculated as minutes of moderate or vigorous physical activity or an equivalent combination per week. According to the guideline, being physically active was defined as engaging in >150 minutes of moderate-intensity activity weekly, >75 minutes of vigorous-intensity activity or a comparable mix of the two.

Table S4. Multivariable-adjusted HRs (95% CIs) of individual social isolation factors for chronic kidney among baseline diabetes patients

Social isolation factors	Chronic kidney disease			
	No. of cases/total	Model 1 HR	Model 2 HR	Model 3 HR
Living alone				
0	831/14 597	1 (Reference)	1 (Reference)	1 (Reference)
1	289/4286	1.11 (0.97 to 1.28)	1.12 (0.98 to 1.29)	1.09 (0.93 to 1.27)
Frequency of social visits				
0	1007/16 799	1 (Reference)	1 (Reference)	1 (Reference)
1	106/2003	0.98 (0.80 to 1.20)	0.98 (0.80 to 1.20)	1.06 (0.85 to 1.32)
Weekly Leisure/social Activities				
0	679/12 148	1 (Reference)	1 (Reference)	1 (Reference)
1	443/6713	1.23 (1.10 to 1.40)	1.17 (1.03 to 1.32)	1.02 (0.89 to 1.18)

Model 1 was adjusted for sex, age, race, Townsend deprivation index.
Model 2: Model 1+ physical activity, healthy diet score, smoking, alcohol use, body mass index.
Model 3: Model 2+ estimated glomerular filtration rate, diabetes duration, the use of diabetes medication, cholesterol-lowering medication, antihypertensive medication, and depression score.

Table S5. Sensitivity analyses of the multivariable-adjusted HRs (95% CIs) of individual loneliness factors for chronic kidney among baseline diabetes patients.

Loneliness factors	Chronic Kidney Disease		
	No. of cases/total	Model 1	Model 1+Social isolation scale
Feeling lonely			
0	813/14 254	1 (Reference)	1 (Reference)
1	299/4361	1.22 (1.04 to 1.43)	1.21 (1.02 to 1.45)
Confiding in someone close			
0	783/13 636	1 (Reference)	1 (Reference)
1	301/4584	1.06 (0.91 to 1.24)	0.96 (0.81 to 1.40)

Model 1 was adjusted for sex, age, race, Townsend deprivation index, physical activity, healthy diet score, smoking, alcohol use, body mass index, estimated glomerular filtration rate, diabetes duration, the use of diabetes medication, cholesterol-lowering medication, antihypertensive medication and depression score. Feeling lonely and confiding in someone close were mutually adjusted in the sensitivity analyses.

Table S6. Stratified analyses for the association between loneliness scale and hazard of chronic kidney disease among baseline diabetes patients.

Subgroups	Loneliness scale				
	0 HR	1 HR	2 HR	*P*-trend	*P* for interaction
Age					0.761
<60 years old	1 (reference)	1.12 (0.80 to 1.57)	1.18 (0.74 to 1.91)	0.412	
≥60 years old	1 (reference)	1.04 (0.87 to 1.24)	1.18 (0.88 to 1.58)	0.313	
Sex					0.332
Women	1 (reference)	1.19 (0.91 to 1.55)	1.35 (0.90 to 2.01)	0.094	
Men	1 (reference)	1.00 (0.82 to 1.22)	1.17 (0.85 to 1.61)	0.483	
Race					0.244
Non-Whites	1 (reference)	1.36 (0.79 to 2.33)	1.76 (0.78 to 3.98)	0.134	
Whites	1 (reference)	1.03 (0.87 to 1.22)	1.19 (0.91 to 1.54)	0.265	
Townsend deprivation index					0.282
Low (Q1)	1 (reference)	1.07 (0.74 to 1.53)	0.55 (0.24 to 1.26)	0.437	
Intermediate (Q2–Q4)	1 (reference)	1.12 (0.91 to 1.37)	1.18 (0.85 to 1.64)	0.213	
High (Q5)	1 (reference)	0.97 (0.68 to 1.39)	1.78 (1.13 to 2.78)	0.061	
Regular physical activity					0.091
No	1 (reference)	0.92 (0.73 to 1.15)	1.12 (0.81 to 1.56)	0.884	
Yes	1 (reference)	1.25 (0.99 to 1.57)	1.32 (0.91 to 1.93)	0.042	
Diet score					0.562
< Median	1 (reference)	1.06 (0.84 to 1.34)	1.15 (0.81 to 1.65)	0.408	
≥ Median	1 (reference)	1.06 (0.85 to 1.32)	1.28 (0.91 to 1.81)	0.209	
Smoking status					0.522
Non-current	1 (reference)	1.03 (0.87 to 1.22)	1.17 (0.90 to 1.53)	0.290	
Current	1 (reference)	1.26 (0.74 to 2.13)	1.74 (0.86 to 3.52)	0.138	
Drinking status					0.703
Non-current	1 (reference)	1.04 (0.70 to 1.53)	0.90 (0.49 to 1.66)	0.867	
Current	1 (reference)	1.06 (0.89 to 1.27)	1.29 (0.99 to 1.70)	0.095	
Obesity					0.077
No	1 (reference)	1.16 (0.91 to 1.48)	1.56 (1.07 to 2.28)	0.026	
Yes	1 (reference)	0.99 (0.80 to 1.22)	1.03 (0.74 to 1.43)	0.954	
eGFR					0.826
<90 mL/min per 1.73 m^2	1 (reference)	1.07 (0.89 to 1.28)	1.21 (0.92 to 1.61)	0.187	
≥90 mL/min per 1.73 m^2	1 (reference)	1.01 (0.72 to 1.43)	1.16 (0.69 to 1.96)	0.654	
Diabetes Duration					0.314
<5 years	1 (reference)	0.93 (0.71 to 1.21)	1.02 (0.67 to 1.56)	0.825	
5-10 years	1 (reference)	1.10 (0.81 to 1.48)	1.27 (0.80 to 2.01)	0.302	
≥10 years	1 (reference)	1.22 (0.93 to 1.59)	1.38 (0.91 to 2.09)	0.085	
Diabetes medication					0.495
No	1 (reference)	1.15 (0.82 to 1.61)	1.55 (0.92 to 2.63)	0.113	
Yes	1 (reference)	1.05 (0.88 to 1.26)	1.17 (0.88 to 1.55)	0.275	
Cholesterol-lowering medication					0.061
No	1 (reference)	0.87 (0.58 to 1.31)	0.54 (0.24 to 1.21)	0.145	
Yes	1 (reference)	1.09 (0.92 to 1.30)	1.36 (1.04 to 1.76)	0.032	
Antihypertensive medication					0.593
No	1 (reference)	0.99 (0.71 to 1.37)	1.17 (0.70 to 1.96)	0.697	
Yes	1 (reference)	1.09 (0.90 to 1.30)	1.26 (0.95 to 1.67)	0.115	
Depressive score					0.824

<3	1 (reference)	1.03 (0.87 to 1.23)	1.23 (0.93 to 1.63)	0.212
≥3	1 (reference)	1.28 (0.75 to 2.18)	1.34 (0.73 to 2.45)	0.343

Model was adjusted for sex, age, race, Townsend deprivation index, physical activity, healthy diet score, smoking, alcohol use, body mass index, estimated glomerular filtration rate, diabetes duration, the use of diabetes medication, cholesterol-lowering medication, antihypertensive medication and depression score.

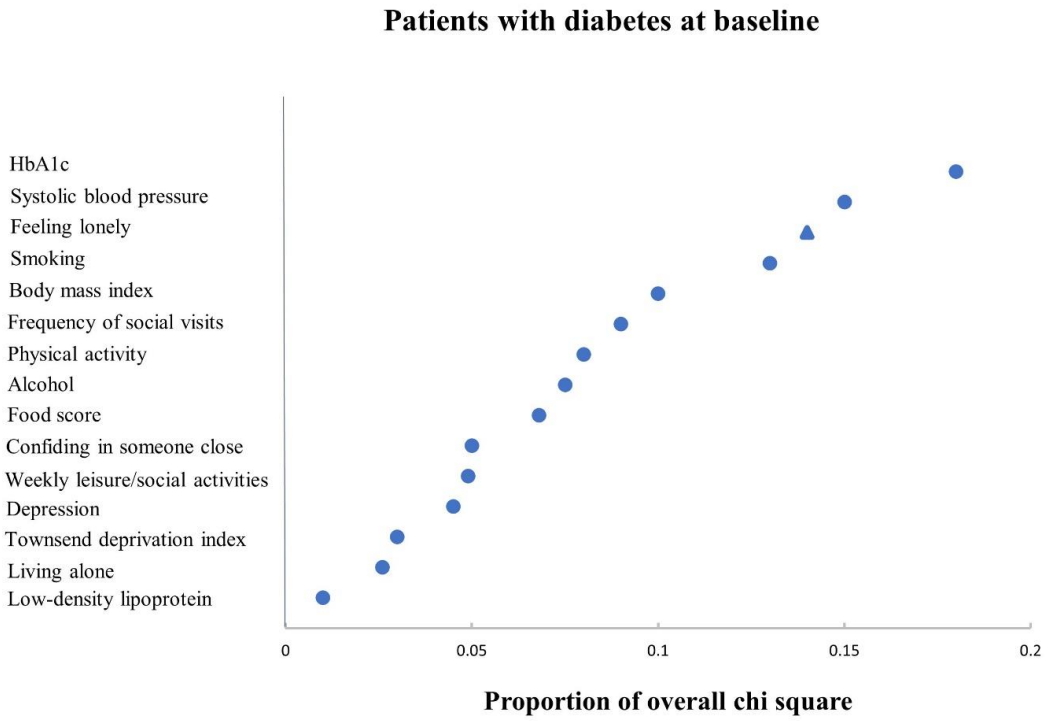

Figure S1. Relative importance of predictors for incident of chronic kidney disease, by estimation of explained log-likelihood explained by each predictor, in patients with diabetes at baseline.