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Association of cardiovascular-kidney-metabolic health and social connection with the risk of depression and anxiety

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Original Article

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Abstract

Background. To explore the association of cardiovascular-kidney-metabolic (CKM) health with the risk of depression and anxiety and to investigate the joint association of CKM health and social connection with depression and anxiety.

Methods. This prospective cohort study included 344 956 participants from the UK Biobank. CKM syndrome was identified as a medical condition with the presence of metabolic risk factors, cardiovascular disease, and chronic kidney disease, and was classified into five stages (stage 0–4) in this study. Loneliness and social isolation status were determined by self-reported questionnaires. Cox proportional hazards models were applied for analyses.

Results. Compared with participants in stage 0, the HRs for depression were 1.17 (95% CI 1.10–1.25), 1.40 (95% CI 1.33–1.48), and 2.14 (95% CI 1.98–2.31) for participants in stage 1, 2–3, and 4, respectively. Similarly, participants in stage 2–3 (HR = 1.20, 95% CI 1.14–1.26) and stage 4 (HR = 1.63, 95% CI 1.51–1.75) had greater risks of incident anxiety. We found additive interactions between loneliness and CKM health on the risk of depression and anxiety. Participants simultaneously reported being lonely and in stage 4 had the greatest risk of depression (HR = 4.44, 95% CI 3.89–5.07) and anxiety (HR = 2.58, 95% CI 2.21–3.01) compared with those without loneliness and in stage 0. We also observed an additive interaction between social isolation and CKM health on the risk of depression.

Conclusions. Our findings suggest the importance of comprehensive interventions to improve CKM health and social connection to reduce the disease burden of depression and anxiety.

Introduction

Depression and anxiety are both prevalent mental illnesses that commonly coexist and are linked to an increased hazard of mortality, as well as an elevated risk of disability, poorer quality of life, and greater financial burden (Chisholm et al., 2016; Druss, Rosenheck, & Sledge, 2000; Machado et al., 2018). According to the World Health Organization reports, 280 and 301 million people were affected by depression and anxiety worldwide in 2019, and the number of individuals suffering from depression and anxiety is rising significantly (World Health Organization, 2017). Given the increased prevalence and the accompanying adverse outcomes of depression and anxiety, identifying and understanding risk factors, particularly the modifiable ones, has significant implications for mitigating the disease burden.

Previous studies have revealed that metabolic disease, cardiovascular disease (CVD), and chronic kidney disease (CKD) are individually related to depression (Bautovich, Katz, Smith, Loo, & Harvey, 2014; Kim, Wolf, & Kim, 2023; Małyszczak & Rymaszewska, 2016; Semenkovich, Brown, Svrakic, & Lustman, 2015; Ziegelstein, 2001). The existing evidence on the associations of these individual diseases with anxiety is limited and mixed (Cen et al., 2024; Huang et al., 2021; Małyszczak & Rymaszewska, 2016). Epidemiological research indicated that metabolic, cardiovascular, and renal diseases often coexist, and growing evidence supported the pathophysiological interactions between these diseases (Grundy, Hansen, Smith, Cleeman, & Kahn, 2004; Marassi & Fadini, 2023; Rangaswami et al., 2019). Recently, the term of cardiovascular-kidney-metabolic (CKM) syndrome has been introduced by the American Heart Association (AHA), which stressed the significance of holistic management of these diseases to prevent the possible adverse consequences (Ndumele et al., 2023). CKM syndrome was classified into five stages to indicate the risk spectrum (Ndumele et al., 2023). However, the associations of CKM syndrome with depression and anxiety remain unclear.

Social isolation and loneliness are significant social determinants representing specific facets of social connection (World Health Organization, 2021a). Social isolation is an objective assessment of social contacts and interactions, while loneliness refers to the personal perception of being socially isolated (Donovan & Blazer, 2020; World Health Organization, 2021b). Existing studies have shown social isolation and loneliness are related to a greater risk of depression and anxiety (Curran, Rosato, Cooper, Mc Garrigle, & Leavey, 2019; Domènech-Abella, Mundó, Haro, & Rubio-Valera, 2019; Zhang et al., 2023). However, the interaction and joint effects of CKM health and social isolation or loneliness on depression and anxiety remain unknown. Understanding the interaction of CKM health with social connection could help clinicians identify vulnerable populations and develop comprehensive preventive strategies for depression and anxiety.

Therefore, this study sought to explore the prospective association of CKM health with the risk of depression and anxiety. We further examined the multiplicative and additive interactions of CKM health with social isolation or loneliness in relation to the risk of depression and anxiety.

Materials and methods

Study population and design

The UK Biobank is a large-scale open-access database with about 0.5 million individuals aged 40–69 years throughout the UK (Palmer, 2007; Sudlow et al., 2015). Baseline socio-demographic, clinical, behavioral factors, biological samples, and other health-related data were collected between 2006 and 2010 (Palmer, 2007; Sudlow et al., 2015). The UK Biobank's ethical approval was granted by the North West Multicenter Research Ethics Committee. All participants gave written informed consent. Participants who lacked data on obesity ($n = 2790$) and metabolic risk factors ($n = 71\,542$) were excluded. Participants who had common mental disorders ($n = 52\,084$) at baseline, only had CVD at baseline ($n = 1681$), or with missing data for covariates ($n = 29\,358$) were excluded. Finally, this study included 344 956 participants in current analyses (online Supplementary Fig. 1). Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (von Elm et al., 2007).

Definition of CKM syndrome

According to the AHA's definition, CKM syndrome was defined as a medical condition caused by connections between obesity, diabetes, CKD, and CVD, and it was categorized into five stages (Ndumele et al., 2023). In our study, stage 0 was defined as normal body mass index and waist circumference, normal glucose, normal blood pressure, normal lipid status, and no evidence of CKD or CVD. Stage 1 was characterized by the existence of equal to or more than one of the following: (1) body mass index ⩾25 kg/m^2; (2) waist circumference ⩾88/102 cm in women/men; (3) fasting blood glucose ⩾100–124 mg/dL or HbA1c between 5.7% and 6.4%; and without other metabolic risk factors, CKD, or CVD. Because of the lack of data on subclinical CVD in the UK Biobank, we cannot discriminate stage 3 from stage 2 and therefore combined the two stages as stage 2–3, which was defined by the presence of hypertriglyceridemia (⩾135 mg/dL), hypertension, metabolic syndrome, diabetes, or CKD. Stage 4 was defined as CVD (heart failure, atrial fibrillation, coronary heart disease, stroke, or peripheral artery disease) overlapping with stages 1–3. Details of the definition of these risk factors or diseases are provided in online Supplementary Table 1.

Definition of social isolation and loneliness

The determination of social isolation status was based on the responses to three questions of whether living alone (yes, no), social contact frequency (⩾once a month, <once a month), and leisure or social activity participation (yes, no) (online Supplementary Table 1) (Elovainio et al., 2023; Hakulinen et al., 2018; Wang et al., 2023). Each question obtained one point, and the overall score varied from 0 to 3, with an increased score representing a greater degree of social isolation. Those who obtained ⩾2 points were classified into the social isolation group. Loneliness was assessed by the question of whether or not they often feel lonely (yes, no) and the frequency of being able to confide to someone (⩾once a month, <once a month) (Elovainio et al., 2023; Hakulinen et al., 2018; Wang et al., 2023). The total loneliness score ranged from 0 to 2 points, and participants who obtained 2 points were classified into the loneliness group (online Supplementary Table 1).

Covariates

We have considered these characteristics as the potential covariates: age, sex (women, men), ethnicity (white, others), Townsend Deprivation Index, education level (degree or above, others), smoking status (never, previous, current), alcohol consumption status (never, previous, current), and moderate to vigorous physical activity (no, yes). Townsend Deprivation Index is a composite measure derived from four dimensions (unemployment, non-car ownership, non-home ownership, and household overcrowding), calculated using census information linked to residents' postcodes, with a higher score indicating a higher degree of deprivation (Townsend, Phillimore, & Beattie, 1988). Detailed descriptions of these covariates are presented in online Supplementary Table 1.

Assessment of outcomes

Incident cases of depression and anxiety were determined through linkage from hospital admission, self-reported data, and death records. Details of the linkage information are provided in Supplementary Method. The follow-up time for each incident case was coded from recruitment to the first diagnosis of depression or anxiety, death date, or last date of follow-up (31 December 2021), whichever occurred first.

Statistical analysis

Differences in participants' characteristics between stages of CKM syndrome were analyzed by analysis of variance (ANOVA) test or χ^2 test. Cumulative incidences of outcomes were calculated by the Kaplan–Meier method. Cox proportional hazard models were fitted to investigate the association of CKM health with incident depression and anxiety. In the base model, we did not adjust for any covariates. In model 2, we adjusted for socio-demographic factors (age, sex, ethnicity, Deprivation Index, and education level) and lifestyle factors (alcohol consumption, smoking status, and physical activity). Then, we further adjusted for social isolation and loneliness.

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We also conducted joint analyses to assess the risk of depression and anxiety among participants with varying degrees of social isolation or loneliness and stages of CKM syndrome, with participants who were in stage 0 and were not isolated (or did not feel lonely) as the reference. Possible multiplicative interactions of social isolation or loneliness on the association of CKM health with depression or anxiety were tested by adding a product term of social isolation or loneliness and CKM heath in the models. We used the relative excess risk due to interaction (RERI) and the attributable proportion (AP) to quantify the additive interaction (Li & Chambless, 2007).

Additionally, some sensitivity analyses were also carried out to assess the robustness of the findings. First, family history of severe depression and annual household income were further adjusted in the multivariate models. Second, we used social isolation and loneliness scores as continuous variables in the models. Third, we included the components of social isolation and loneliness in the adjusted models. Fourth, we conducted Fine–Gray analyses in consideration of death as a competing event (Austin, Lee, & Fine, 2016). We adjusted for socio-demographic factors and lifestyle factors in the model, and we further adjusted for social isolation and loneliness. Fifth, we excluded incident depression or anxiety cases within the first 2 years of follow-up. Sixth, for covariates with the selection of 'do not know' or 'prefer not to answer', a separate category was created. Subgroup analyses were also performed to test the possible modification effects of age, sex, ethnicity, Deprivation Index, and education level.

A two-sided $p < 0.05$ indicates statistical significance. All analyses were conducted using SAS version 9.4.

Results

Overall, 344 956 participants were involved in this study (online Supplementary Fig. 1). The mean age of participants was 56.6 ± 8.1 years, and 52.7% were women. At baseline, 58 553 (17.0%), 70 508 (20.4%), 191 548 (55.5%), and 24 347 (7.1%) participants were in stage 0, 1, 2–3, and 4 of CKM syndrome, respectively. Table 1 illustrates the distribution of participants' characteristics according to stages of CKM syndrome. Participants in later stages were older, having a higher proportion of men, lower levels of education, and more health risk factors (smoking and insufficient physical activity), and were more likely to experience social isolation and loneliness (Table 1).

Associations of CKM health with incident depression and anxiety

Over a median follow-up of 12.8 years (IQR 12.0–13.5 years), we identified 12 582 (3.7%) and 14 267 (4.1%) incident cases of depression and anxiety, respectively. The cumulative incidence of outcomes was highest in stage 4 (log-rank $P < 0.001$) compared with earlier stages (online Supplementary Table 2 and Fig. 2). The associations of CKM stages with depression and anxiety displayed dose–gradient relationships (both $P_{trend} < 0.001$) (Table 2). After adjustment for socio-demographic factors and lifestyle factors, compared with participants in stage 0, the HRs for depression were 1.18 (95% CI 1.10–1.25, $P < 0.001$), 1.42 (95% CI 1.34–1.50, $P < 0.001$), and 2.20 (95% CI 2.05–2.38, $P < 0.001$) for participants in stage 1, 2–3, and 4, respectively. Similarly, participants in stage 2–3 (HR = 1.21, 95% CI 1.15–1.27, $P < 0.001$) and stage 4 (HR = 1.65, 95% CI 1.54–1.78, $P < 0.001$) had a greater risk of incident anxiety when adjusting for socio-demographic and lifestyle factors. The associations did not alter after including social isolation and loneliness in the models (Table 2).

Joint associations of social isolation or loneliness and CKM health with incident depression and anxiety

In Fig. 1, the joint associations of social isolation and the stage of CKM syndrome with the risk of depression and anxiety have been shown. Compared with the reference group, individuals with social isolation and in stage 4 had an adjusted HR of 2.37 (95% CI 2.05–2.73, $P < 0.001$) and an adjusted HR of 1.91 (95% CI 1.64–2.22, $P < 0.001$) for incident depression and anxiety, respectively (Fig. 1). Participants reported being lonely and in stage 4 had a 344% greater risk of depression (HR = 4.44, 95% CI 3.89–5.07, $P < 0.001$) and 158% higher risk of anxiety (HR = 2.58, 95% CI 2.21–3.01, $P < 0.001$) (Fig. 2). An additive interaction was observed between social isolation and the stage of CKM syndrome on the risk of depression (RERI = 0.11, 95% CI 0.04–0.17; AP = 0.06, 95% CI 0.04–0.09, $P = 0.003$) (online Supplementary Table 3). We also found additive interactions between loneliness and CKM health on the risk of depression (RERI = 0.42, 95% CI 0.34–0.50; AP = 0.14, 95% CI 0.10–0.17, $P < 0.001$) and anxiety (RERI = 0.17, 95% CI 0.09–0.25; AP = 0.10, 95% CI 0.08–0.13, $P < 0.001$) (online Supplementary Table 4). We did not observe a significant multiplicative interaction between social isolation or loneliness and the stage of CKM syndrome on incident depression and anxiety (online Supplementary Tables 5 and 6).

Subgroup and sensitivity analyses

After adjustment for family history of severe depression or annual household income, the association of CKM health with depression and anxiety remained consistent (online Supplementary Tables 7 and 8). When treating social isolation score and loneliness score as continuous variables, consistent results have been found (online Supplementary Table 9). When adjusting components of social isolation and loneliness in the models, the results remained similar (online Supplementary Table 10). Consistent results have been yielded when considering the competing risk of death (online Supplementary Table 11). The HRs did not substantially alter when excluding incident depression or anxiety cases during the initial 2 years of follow-up (online Supplementary Table 12). When defining 'do not know/ prefer not to answer' in a separate category for some covariates, no substantial change in the association has been observed (online Supplementary Table 13). We did not find the modification effects of most covariates on the association of CKM heath with depression and anxiety, except ethnicity (online Supplementary Tables 14 and 15).

Discussion

In this prospective cohort study of 344 956 participants from the UK Biobank, we observed dose–response associations between stages of CKM syndrome with depression and anxiety. Compared with participants in stage 0, those in later stages had greater risks of incident depression and anxiety. Significant additive interactions between CKM health and loneliness in relation to depression and anxiety have been observed. A significant additive interaction between CKM health and social isolation on the risk of depression has also been detected. From a public health

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Table 1. Baseline characteristics of participants according to stage of CKM syndrome

	Total	Stage 0	Stage 1	Stage 2–3	Stage 4	*P*-for-difference value
N	344 956	58 553	70 508	191 548	24 347	
Age (years), mean (s.d.)	56.6 ± 8.1	53.6 ± 8.1	55.0 ± 8.2	57.4 ± 7.8	61.8 ± 6.1	<0.001
Sex						<0.001
Women	181 741 (52.7)	41 503 (70.9)	42 602 (60.4)	90 033 (47.0)	7603 (31.2)	
Men	163 215 (47.3)	17 050 (29.1)	27 906 (39.6)	101 515 (53.0)	16 744 (68.8)	
Deprivation Index, mean (s.d.)	−1.5 ± 3.0	−1.7 ± 2.9	−1.5 ± 2.9	−1.4 ± 3.0	−1.0 ± 3.2	<0.001
Ethnicity						<0.001
White	329 221 (95.4)	56 836 (97.1)	66 727 (94.6)	182 317 (95.2)	23 341 (95.9)	
Others	15 735 (4.6)	1717 (2.9)	3781 (5.4)	9231 (4.8)	1006 (4.1)	
Education level						<0.001
Degree or above	133 796 (38.8)	28 559 (48.8)	28 678 (40.7)	69 525 (36.3)	7034 (28.9)	
Others	154 815 (44.9)	24 926 (42.6)	32 501 (46.1)	87 399 (45.6)	9989 (41.0)	
Unknown	56 345 (16.3)	5068 (8.7)	9329 (13.2)	34 624 (18.1)	7324 (30.1)	
Smoking status						<0.001
Current	33 653 (9.8)	4916 (8.4)	5880 (8.3)	20 156 (10.5)	2701 (11.1)	
Former	120 503 (34.9)	16 751 (28.6)	23 082 (32.7)	68 765 (35.9)	11 905 (48.9)	
Never	190 800 (55.3)	36 886 (63.0)	41 546 (58.9)	102 627 (53.6)	9741 (40.0)	
Alcohol consumption						<0.001
Current	321 104 (93.1)	55 322 (94.5)	66 427 (94.2)	177 613 (92.7)	21 742 (89.3)	
Former	10 561 (3.1)	1447 (2.5)	1704 (2.4)	6047 (3.2)	1363 (5.6)	
Never	13 291 (3.9)	1784 (3.0)	2377 (3.4)	7888 (4.1)	1242 (5.1)	
Moderate to vigorous activity						<0.001
Yes	273 429 (79.3)	49 222 (84.1)	57 537 (81.6)	148 499 (77.5)	18 171 (74.6)	
No	71 527 (20.7)	9331 (15.9)	12 971 (18.4)	43 049 (22.5)	6176 (25.4)	
Social isolation						<0.001
Yes	29 111 (8.4)	4368 (7.5)	5198 (7.4)	16 945 (8.9)	2600 (10.7)	
No	315 845 (91.6)	54 185 (92.5)	65 310 (92.6)	174 603 (91.2)	21 747 (89.3)	
Loneliness						<0.001
Yes	18 620 (5.4)	2541 (4.3)	3396 (4.8)	10 821 (5.7)	1862 (7.6)	
No	326 336 (94.6)	56 012 (95.7)	67 112 (95.2)	180 727 (94.3)	22 485 (92.4)	
Systolic blood pressure	138.3 ± 18.6	128.6 ± 17.0	134.4 ± 17.5	142.5 ± 18.1	139.9 ± 18.8	<0.001
Diastolic blood pressure	82.4 ± 10.1	77.2 ± 9.1	80.9 ± 9.4	84.8 ± 9.9	80.7 ± 10.5	<0.001

Body mass index	27.3 ± 4.7	22.5 ± 1.7	27.2 ± 3.4	28.6 ± 4.7	29.3 ± 4.9	<0.001
Waist circumference	90.2 ± 13.3	76.4 ± 7.7	87.9 ± 10.4	94.2 ± 12.5	98.1 ± 13.0	<0.001
HDL-C	56.2 ± 14.8	66.1 ± 14.7	61.6 ± 13.9	52.0 ± 13.0	48.7 ± 13.1	<0.001
HbA1C	5.4 ± 0.6	5.2 ± 0.3	5.3 ± 0.4	5.5 ± 0.7	5.8 ± 0.8	<0.001

HDL-C, High density lipoprotein cholesterol.
Note: ANOVA and χ^2 test were used to test the differences among categories for continuous and categorical variables, respectively.

perspective, these findings suggested that improving CKM health could potentially serve as an effective strategy for preventing depression and anxiety, underlining the importance of assessing CKM health and identifying individuals in later CKM stages, as they had an increased likelihood of developing depression and anxiety. Our findings also implied the necessity of a comprehensive and targeted approach to promote CKM health and social connection simultaneously to improve mental health.

Our study is the first demonstration of the significant association of CKM health with depression and anxiety. The existing studies have shown the association of individual diseases (including diabetes, coronary heart disease, and CKD) with an increased risk of depression (Bautovich et al., 2014; Kim et al., 2023; Małyszczak & Rymaszewska, 2016; Semenkovich et al., 2015; Ziegelstein, 2001). Some previous studies also reported the relationship between cardiometabolic disease and greater risks of depression (Gong et al., 2022; Huang et al., 2022; Ronaldson et al., 2021). A cross-sectional study suggested a cumulative dose-dependent connection between the number of cardiometabolic diseases and depression; participants with more than three conditions of cardiometabolic disease had a 113% greater risk of depression (Gong et al., 2022). The China Health and Retirement Longitudinal Study suggested the increasing number of cardiometabolic diseases was related to depressive symptoms (Huang et al., 2022). Conclusions on the impact of individual diseases on anxiety are inconsistent. For example, some previous investigations did not show a correlation between diabetes and incident anxiety over more than 10 years of follow-up (Engum, 2007; Marrie et al., 2016); however, another study observed diabetes was related to 2.6 times increased risk of anxiety disorder among Australian women (Hasan, Clavarino, Dingle, Mamun, & Kairuz, 2015). Several studies showed that metabolic syndrome was not related to a greater risk of anxiety (Skilton, Moulin, Terra, & Bonnet, 2007; Takeuchi et al., 2009), whereas some other studies reported a significant association of metabolic syndrome with anxiety (Cen et al., 2024; Ji et al., 2023). In our study, compared with participants without CKM risk factors (stage 0), those with metabolic risk factors (stage 1), with metabolic risk factors plus CKD (stage 2–3), and with concomitant metabolic disease, CKD, and CVD (stage 4) had 17, 40, and 114% greater risk of depression. We also observed that participants in stage 2–3 and 4 of CKM syndrome had greater risks of anxiety compared with those in stage 0. These findings reveal that it might be feasible to focus on implementing stage-specific strategies to halt or delay the development of CKM syndrome, especially to prevent CVD, to decrease the likelihood of developing depression and anxiety.

Accumulating evidence indicates that the pathophysiological mechanisms of metabolic disease, CVD, and CKD are interrelated. For instance, metabolic syndrome is correlated to the development of nearly all CVD subcategories (Wilson, D'Agostino, Parise, Sullivan, & Meigs, 2005); type 2 diabetes has the potential to result in renal and vascular damage (Burrows, Koyama, & Pavkov, 2022); and CKD plays a significant role in amplifying cardiovascular risk (Go, Chertow, Fan, McCulloch, & Hsu, 2004; van der Velde et al., 2011). Currently, an AHA presidential advisory put forward the concept of CKM syndrome and emphasized the efforts to enhance CKM care (Ndumele et al., 2023). Several potential mechanisms have been proposed for the relationship between CKM syndrome and depression and anxiety. CKM syndrome could be related to a greater risk of symptom burden, frailty, chronic pain, and decreased quality of life, which could

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Table 2. Association of stages of CKM syndrome with risk of depression and anxiety

	Model 1[a]		Model 2[b]		Model 3[c]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Depression						
Stage 0	1.00		1.00		1.00	
Stage 1	1.16 (1.09–1.24)	<0.001	1.18 (1.10–1.25)	<0.001	1.17 (1.10–1.25)	<0.001
Stage 2-3	1.41 (1.33–1.48)	<0.001	1.42 (1.34–1.50)	<0.001	1.40 (1.33–1.48)	<0.001
Stage 4	2.26 (2.11–2.43)	<0.001	2.20 (2.05–2.38)	<0.001	2.14 (1.98–2.31)	<0.001
P_{trend}	<0.001		<0.001		<0.001	
Anxiety						
Stage 0	1.00		1.00		1.00	
Stage 1	1.03 (0.97–1.09)	0.315	1.05 (0.99–1.11)	0.085	1.05 (0.99–1.11)	0.091
Stage 2-3	1.15 (1.09–1.20)	<0.001	1.21 (1.15–1.27)	<0.001	1.20 (1.14–1.26)	<0.001
Stage 4	1.57 (1.46–1.68)	<0.001	1.65 (1.54–1.78)	<0.001	1.63 (1.51–1.75)	<0.001
P_{trend}	<0.001		<0.001		<0.001	

CI, confidence interval; CKM, cardiovascular-kidney-metabolic; HR, hazard ratio.
[a]Model 1 was not adjusted for covariates.
[b]Model 2 was adjusted for age, sex, ethnicity, Deprivation Index, education level, smoking status, alcohol consumption, and physical activity.
[c]Model 3 was adjusted for age, sex, ethnicity, Deprivation Index, education level, smoking status, alcohol consumption, physical activity, social isolation, and loneliness.

result in increased emotional burden (Katon, Lin, & Kroenke, 2007; Makovski, Schmitz, Zeegers, Stranges, & van den Akker, 2019; Sharpe et al., 2017; Soysal et al., 2017; Vetrano et al., 2019). Additionally, inflammation has been recognized as a major pathological factor behind depression and anxiety, and most chronic physical diseases are marked by a significant inflammatory burden (Guo et al., 2023; Shao et al., 2020; Yang et al., 2021). Besides, dysregulation of the hypothalamic-pituitary-adrenal axis may contribute to the development of depression among individuals with CKM syndrome (Belvederi Murri et al., 2014). Given the complexity of the interrelation between cardiovascular, metabolic, and kidney diseases, comprehensive management approaches to these diseases should be undertaken to reduce the disease burden of mental disorders. Further investigation is needed to elucidate the pathways involved in the association of CKM health with depression and anxiety.

The current study observed a substantial additive interaction, which has more public health significance than multiplicative interaction, between CKM health and social isolation in relation to depression. We also found that the combination of poor CKM health and loneliness might act synergistically to increase the risk of depression and anxiety. With growing public health concerns about social isolation and loneliness, the World Health Organization has launched the Commission on Social Connection (2024–2026) to tackle the urgent global health threats (World Health Organization, 2023). Strong evidence has shown that the lack of social connection enhances the hazard of physical and mental problems, such as depression and anxiety (World

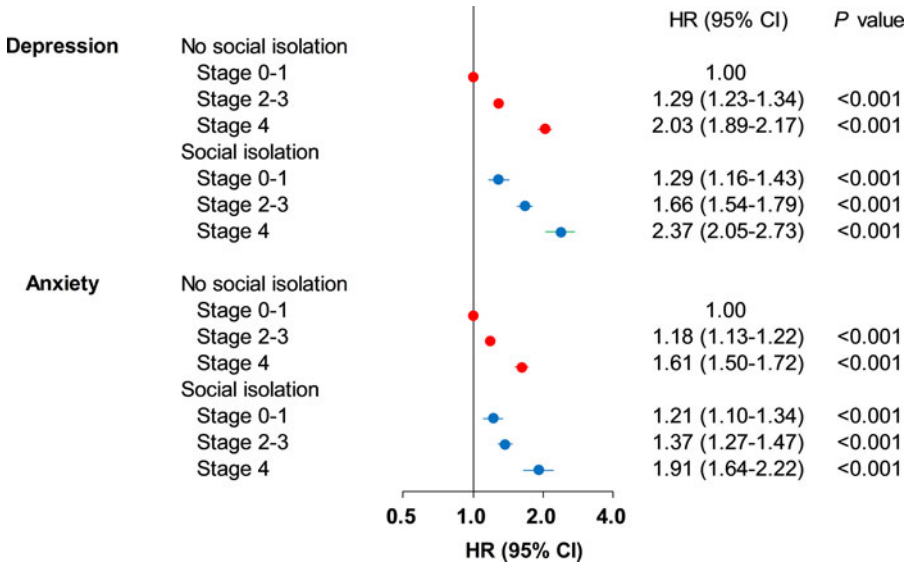

Figure 1. Joint associations of social isolation and the stage of CKM syndrome with incident depression and anxiety. HRs were adjusted for age, sex, ethnicity, Deprivation Index, education level, smoking status, alcohol consumption, and physical activity. CKM, cardiovascular-kidney-metabolic; CI, confidence interval; HR, hazard ratio.

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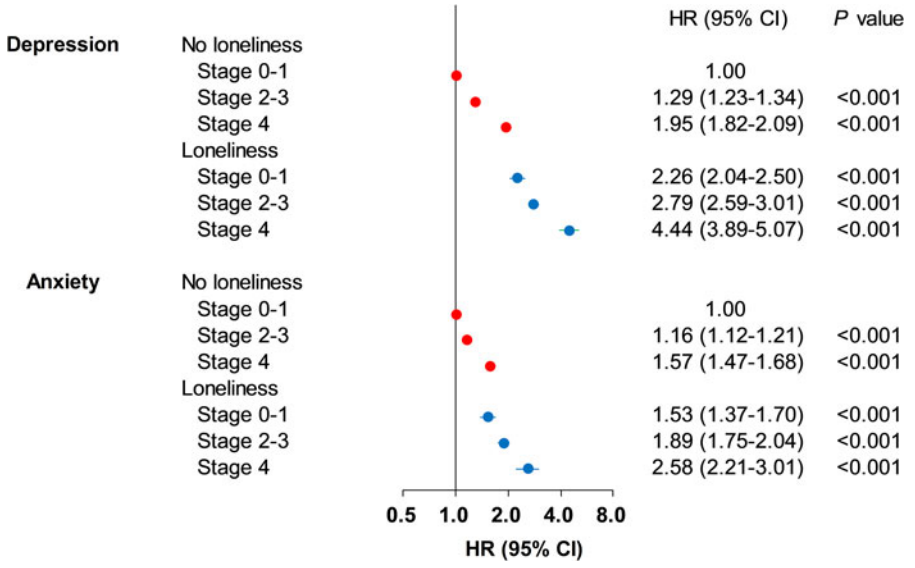

Figure 2. Joint associations of loneliness and the stage of CKM syndrome with incident depression and anxiety. HRs were adjusted for age, sex, ethnicity, Deprivation Index, education level, smoking status, alcohol consumption, and physical activity. CKM, cardiovascular-kidney-metabolic; CI, confidence interval; HR, hazard ratio.

Health Organization, 2023). However, this is the first attempt to examine the interaction and joint effect of social connection and CKM health on depression and anxiety. Specifically, the concurrence of stage 4 of CKM syndrome and loneliness could lead to an additional 14% and 10% of cases of depression and anxiety, respectively. Our findings underscore the significance of public health countermeasures to promote CKM health, especially among those with loneliness or social isolation. Additionally, more collaborative action should be taken to implement effective interventions to mitigate the impact of social isolation and loneliness.

Strengths and limitations

This study has some major strengths. To our knowledge, this is the first investigation of the association of CKM heath with depression and anxiety. We evaluated both multiplicative and additive interactions between CKM health and social connection in relation to depression and anxiety. Our findings could provide valuable information for clinicians to identify vulnerable populations at an increased risk of depression and anxiety. The large sample size and long follow-up period of the UK Biobank allowed us to perform the stratified analyses with sufficient statistical power, and we observed consistent results in most subpopulations.

Nevertheless, it is important to interpret our findings with caution due to some limitations. First, the nature of observational study poses challenges in establishing the causal relationship, even if the results in sensitivity analysis were consistent when excluding incident cases during the initial 2 years of follow-up. Second, although this study has adjusted for various potential confounders, there could be unmeasured or residual confounding. Third, because there is insufficient data on subclinical CVD in the UK Biobank, we are unable to separate participants with subclinical CVD in CKM syndrome (defined as stage 3 of CKM syndrome by the AHA) (Ndumele et al., 2023); therefore, we combined stage 3 with stage 2 as stage 2–3 in our study. Fourth, social isolation and loneliness were defined by some simple questions. Nevertheless, the questions used in our study have been modified from validated scales and applied in other research (Elovainio et al., 2023; Hakulinen et al., 2018; Wang et al., 2023). Fifth, the study participants in the UK Biobank were recruited from a community context, which may introduce participation bias, as this population is likely to be more affluent and healthier than the general UK population. Consequently, the effect sizes reported in this study may represent conservative estimates. Last, the majority of individuals in this study were of European descent, and the generalizability of our study results to other ethnic groups could be limited.

Conclusion

Our study suggested that poor CKM health was independently associated with an increased risk of depression and anxiety. Besides, we found significant additive interactions between loneliness or social isolation and the stage of CKM syndrome. These findings support the importance of comprehensive interventions to simultaneously promote CKM health and social connection in improving mental health.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724002381.

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Competing interests. None.

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