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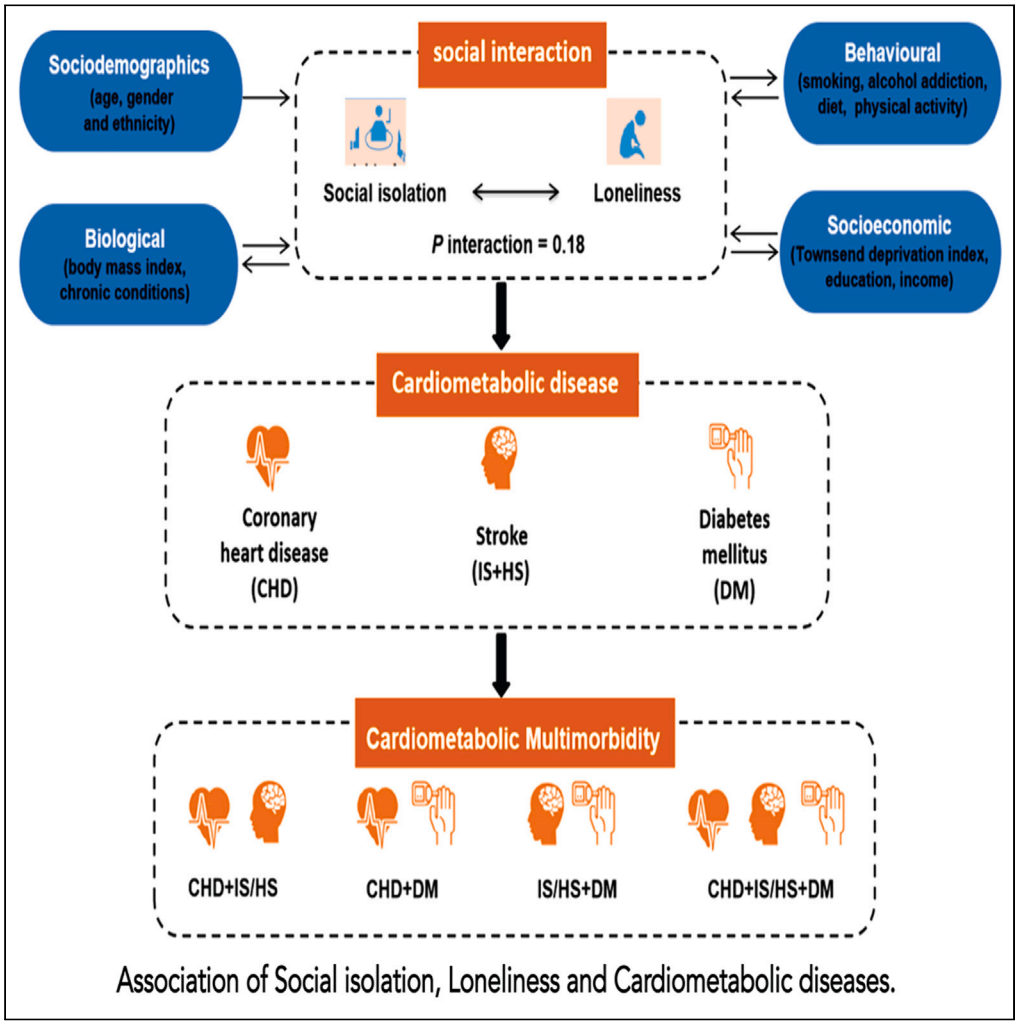

Association of Social isolation, Loneliness and Cardiometabolic diseases.

Zhilin Xiao, Jing Li, Yi Luo, Liu Yang, Guogang Zhang, Xunjie Cheng, Yongping Bai

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Highlights

The prevalence of social isolation/loneliness was increased due to COVID-19

Social isolation was associated with increased risk of CMD and CMM

Social loneliness was associated with increased risk of CMD and CMM

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Social isolation and loneliness with risk of cardiometabolic multimorbidity: A prospective cohort study from UK Biobank

Zhilin Xiao,[1,2,6] Jing Li,[1,2,3,6] Yi Luo,[1,2] Liu Yang,[1,2] Guogang Zhang,[4] Xunjie Cheng,[1,2,*] and Yongping Bai[1,2,5,7,*]

SUMMARY

The pandemic of the coronavirus disease 2019 resulted in an increased prevalence of social isolation and loneliness. Cox proportional hazards regression was used to test the association between social isolation/loneliness, multiple cardiometabolic diseases (CMDs) and cardiometabolic multimorbidity (CMM). In the multivariable adjusted models, compared with the least isolated, the most isolated had independently associated with CMD (HR 1.07, 95% CI 1.03 to 1.11) and CMM (HR 1.24, 95% CI 1.12 to 1.36) in stage I, and CMM in stage II (HR 1.14, 95% CI 1.05 to 1.23). Compared with those with the least loneliness, those who with most loneliness had about 20% increased risk of CMD and 29% increased risk of CMM in stage I. Those with the most loneliness were also significantly associated with increased CMM risk (HR 1.30, 95% CI 1.19 to 1.42) in stage II. This study revealed the associations of social isolation/loneliness with CMD and CMM.

INTRODUCTION

With population aging, the prevalence of multimorbidity, referring to the coexistence of two or more long-term conditions, is increasing rapidly and has become a global public health challenge.[1,2] Cardiometabolic multimorbidity (CMM), one kind of the most common multimorbidity, defined as the coexistence of at least two cardiometabolic diseases (CMDs), including stroke, coronary heart disease (CHD), and diabetes mellitus (DM), has been proved to be associated with multiplicative mortality risk.[3–5] For example, at the age of 60, people with one CMD had a 2-fold increase in mortality risk and a life expectancy 6–10 years shorter than those without CMD, whereas people with CMM had a 4- to 8-fold increase in mortality risk and a life expectancy shorter by up to 15 years.[6]

Social and demographic changes have led to an increased prevalence of social isolation and loneliness in modern society.[7,8] Though social isolation is important to slow the spread of COVID-19, it has led to increased loneliness.[9] 24% of older adults aged 65 and above are considered as socially isolated,[10] and around half of all adults in the US, the UK, and Australia are lonely.[11–13] Therefore, political stakeholders have considered them as serious public health concerns.[14] Although isolated and lonely persons are at increased risk of all-cause and CVD-specific mortality,[15,16] the association between social isolation and CHD or stroke is inconclusive. Several studies suggested that social isolation increased the risk of incidental CHD. For example, people with low social participation had about 4.6 times higher incidence rates of CHD than those who enjoyed high social participation in a follow-up study of 6900 participants in Sweden,[17] and in a cohort study of 57, 825 older women from the US, there was a linear correlation between social isolation and incidental cardiovascular disease (CVD).[18] However, other large UK prospective studies found that social isolation had little direct effect on the risk of developing CHD or stroke, and the association between social isolation and CHD risk appeared to be largely or wholly explained by personal characteristics of the participants after adjusting for confounding factors.[19] By contrast, social isolation substantially increased the risk of a first fatal CHD or stroke event, particularly among people who live alone.[20,21]

With the outbreak of the COVID-19 pandemic, there has been growing interest in loneliness as a psychosocial risk factor and social isolation as a behavioral risk factor both for physical and mental health. However, the existing fragmented studies were conducted by only focusing on certain group individuals and on one stage of disease progression. As far as we know, the associations of social isolation and loneliness with CMM remain totally unexplored, making it challenging to compare the impact of social isolation and loneliness on different stages before and after single CMD. Therefore, we aimed to examine whether the deficiency of social participation and loneliness increases the risk of incidental CMD and CMM in a large UK prospective observational cohort, and try to explore some intervention strategies for CMDs. Here, data

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Table 1. Baseline characteristics of participants

Characteristic	Stage I (n = 343425)				Stage II (n = 35209)		
	Free of any Disease	Healthy to CMD	Healthy to CMM	p value	Yes	No	p value
Number of participants (%)	304362 (88.6)	34589 (10.1)	4474 (1.3))		6981 (19.8)	28228 (80.2)	<0.001
Age (years) (mean (SD))	55.67 (8.03)	59.65 (7.25)	61.29 (6.69)	<0.001	62.06 (6.31)	60.33 (7.05)	<0.001
Female (%)	173229 (56.9)	14159 (40.9)	1633 (36.5)	<0.001	2106 (30.2)	10723 (38.0)	0.074
White ethnicity (%)	292931 (96.2)	33185 (95.9)	4221 (94.3)		6560 (94.0)	26683 (94.5)	<0.001
Townsend Deprivation Index (mean (SD))	−1.54 (2.93)	−1.24 (3.12)	−0.89 (3.27)	<0.001	−0.65 (3.33)	−1.02 (3.20)	<0.001
Body mass index, kg/m^2	26.81 (4.42)	28.64 (5.05)	29.63 (5.31)	<0.001	30.70 (5.55)	29.36 (5.34)	<0.001
Physical activity (%)	240124 (78.9)	26564 (76.8)	3362 (75.1)	<0.001	5040 (72.2)	21306 (75.5)	<0.001
Drinking ≥3 times/week (%)	142991 (47.0)	15414 (44.6)	1823 (40.7)	<0.001	2621 (37.5)	11424 (40.5)	<0.001
Ideal healthy diet, n (%)	170773 (56.1)	18229 (52.7)	2277 (50.9)	<0.001	3784 (54.2)	15993 (56.7)	<0.001
Current smoker, n (%)	28943 (9.5)	4768 (13.8)	736 (16.5)	<0.001	990 (14.2)	3042 (10.8)	
Education (%)				<0.001			<0.001
Poor	69196 (22.7)	11359 (32.8)	1756 (39.2)	<0.001	2927 (41.9)	9903 (35.1)	
Intermediate	103543 (34.0)	10932 (31.6)	1368 (30.6)		2077 (29.8)	8701 (30.8)	
High	131623 (43.2)	12298 (35.6)	1350 (30.2)		1977 (28.3)	9624 (34.1)	<0.001
Antihypertensive medications (%)	40504 (13.3)	9226 (26.7)	1690 (37.8)	<0.001	4714 (67.5)	15820 (56.0)	<0.001
Cholesterol-lowering medications, n (%)	26801 (8.8)	6350 (18.4)	1154 (25.8)	<0.001	5289 (75.8)	19679 (69.7)	<0.001
High income level (%)	174596 (57.4)	15117 (43.7)	1551 (34.7)	<0.001	2101 (30.1)	10985 (38.9)	<0.001
Aspirin (%)	22814 (7.5)	4600 (13.3)	842 (18.8)	<0.001	4190 (60.0)	15669 (55.5)	<0.001

CMD, Cardiometabolic diseases; CMM, Cardiometabolic Multimorbidity.

analysis was divided into two parts: (1) stage I: from a healthy state (i.e., without any CMD at baseline) to single CMD (any one of DM, stroke, and CHD) and CMM; (2) stage II: from single CMD (i.e., with any one of DM, stroke, and CHD at baseline) to CMM.

RESULTS

Baseline characteristics

A total of 343,425 participants from UK Biobank free of any CMD at baseline were included in stage I. During a median follow-up of 12.3 years, 34,589 participants (10.1%) and 4,474 participants (1.3%), who were more likely to be women and older, obese, current smokers, and low educated, developed single CMD (without progressing to the next disease) and CMM respectively. They also showed lower rates of physical activity, heavy drinking, healthy eating, and high income. In addition, they were more inclined to reside in a deprived area and take chronic diseases-related medicines such as anti-hypertensive drugs (Table 1).

A total of 35,209 participants with a diagnosis of single CMD at baseline were included in stage II. During a median follow-up of 11.8 years, 6981 individuals (19.9%) developed CMM, who tended to be old, poorly educated, and with less alcohol intake frequency, but less likely to be of white ethnicity, physically active, healthy eating, and high earning. Meanwhile, they possessed higher BMI and Townsend scores (Table 1).

Social isolation

Figures S2 and S3 showed that the cumulative survival curves of the transitions from healthy or one-CMD to CMM was significantly higher in the least isolated/loneliness than in the most isolated/loneliness.

In Cox proportional hazards models, the minimally adjusted hazard ratios (model 1) for the risk of single CMD and CMM from healthy among the most socially isolated people compared with the least isolated counterparts were 1.29 (95% CI 1.25 to 1.34) and 1.71 (1.56–1.88), respectively. The association was attenuated by 14% and 29% after further adjustment for biological and behavioral factors (model 2), and by 8% and 18% after further adjustment for socioeconomic risk factors (model 3). In stage II, social isolation independently increased the risk of being diagnosed with CMM by 14% (Table 2). Subgroup analyses by sex, age, BMI, Townsend index, physical activity, and diet, most of those isolated still possessed stronger association with single CMD and CMM, and these were more prone to influence women, those under 60, and those with poor diet habits during the transition from CMD-free to single CMD (Figure 1A). Also, the unfavorable association of most isolated with cardiometabolic outcomes was stronger in the subgroup of poor eating than that of ideal eating (Figure 1C, *P* for interaction = 0.002). In the sensitivity analysis testing for reverse-causation bias and adjusting for loneliness and depression, additionally, the association of social isolation with single CMD and CMM was consistent with the main findings (Tables S4–S6). Meanwhile, it was important to

Table 2. Associations between the three levels of social isolation and different cardiometabolic endpoints in Stage I and Stage II

		Model 1		Model 2		Model 3	
Variable		HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Stage I	**Healthy to CMD (n = 34,589)**						
	Least isolated	1.00		1.00		1.00	
	Moderately isolated	1.11 (1.09, 1.14)	<0.001	1.05 (1.03, 1.08)	<0.001	1.02 (0.99, 1.04)	0.147
	Most isolated	1.29 (1.25, 1.34)	<0.001	1.15 (1.11, 1.20)	<0.001	1.07 (1.03, 1.11)	<0.001
	Healthy to CMM (n = 4,474)						
	Least isolated	1.00		1.00		1.00	
	Moderately isolated	1.23 (1.15, 1.31)	<0.001	1.12 (1.05, 1.20)	<0.001	1.05 (0.99, 1.12)	0.125
	Most isolated	1.71 (1.56, 1.88)	<0.001	1.42 (1.29, 1.56)	<0.001	1.24 (1.12, 1.36)	<0.001
Stage II	**CMD to CMM (n = 6,981)**						
	Least isolated	1.00		1.00		1.00	
	Moderately isolated	1.17 (1.11, 1.23)	<0.001	1.11 (1.05, 1.16)	<0.001	1.07 (1.02, 1.13)	0.008
	Most isolated	1.39 (1.29, 1.49)	<0.001	1.22 (1.13, 1.32)	<0.001	1.14 (1.05,1.23)	<0.001

Model 1 was adjusted for age, sex and ethnicity.
Model 2 was additionally adjusted for BMI, smoking status, alcohol consumption, physical activity, and healthy diet.
Model 3 was further adjusted for Townsend deprivation index, education, income, antihypertensive drug use, lipid-lowering drug use, and aspirin use.
CMD, Cardiometabolic diseases; CMM, Cardiometabolic Multimorbidity; HR, hazard ratio; CI, confidence interval.

note the bidirectional associations between social isolation and loneliness, and in our analysis, Spearman's correlation coefficient indicated no statistically significant correlation between social isolation and loneliness (r = 0.18, data are not shown). Results from multistate models revealed that social isolation was associated significantly with the risk of CMDs developing and subsequent transitions to CMM. The HR and 95% CI values of all transitions are shown in Figure S4.

For single CMD outcome in stage I, social isolation only independently increased the risk of incidental DM and stroke by 11% and 12%. According to the minimally adjusted model, people who were the most isolated had a significantly higher HR (1.17, 95% CI: 1.11–1.23; 17% higher risk) for CHD, which was attenuated completely after full adjustment (HR 1.02, 95% CI: 0.97–1.08) (Tables S7).

Loneliness

In Cox proportional hazards models, the minimally adjusted (model 1) HRs for the association of most vs. least loneliness with incidental single CMD and CMM in stage I were 1.44 (95% CI 1.38 to 1.51) and 1.75 (95% CI 1.55 to 1.98), respectively. The association was attenuated by 17% and 33% in model 2, and further attenuated by 7% and 13% (20% and 29% independent higher risk, respectively) in model 3 (Table 3). In stage II, loneliness was still independently associated with higher risk of onset CMM (HR 1.30, 95% CI 1.19–1.42, 30% higher risk) (Table 3). This association was consistent across age, sex, BMI, and Townsend index subgroups, although it was stronger in women than in men in stage I (Figures 2A and 2B). Notably, most loneliness increased risk for CMD more significantly in aged person over 60, but that for CMM in people under 60 (*P* for interaction = 0.001). Moreover, the unfavorable association of most loneliness with CMM was stronger in people with a poor diet habit than that in people with an ideal healthy diet (Figure 2). For CMD-specific outcome in stage I, loneliness independently increased the risk of incident DM, stroke, and CHD by 21%, 17%, and 19%, respectively (Table S12).

In the sensitivity analyses by adjusting for social isolation, depression, and excluding new cases with CMD and CMM within 2 years, the associations between loneliness and single CMD and CMM held even (Tables S9–S11). Results from multistate models revealed that loneliness was associated with each stage of CMM developing, including the transitions from CMD-free to first occurrence of cardiometabolic diseases (FCMD), and ultimately to CMM (Figure S5).

In addition, we analyzed the associations of high-risk factors (i.e., living alone, less social contact, less social activities, feeling lonely, and less confiding to close people, that are related to the scales of social isolation and loneliness) with different cardiometabolic endpoints and found they had different risk associations with single CMD and CMM (Table S3).

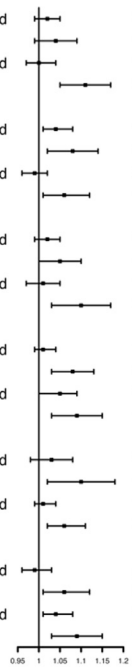
DISCUSSION

Overall, this large prospective study of UK Biobank provides strong evidence that social isolation and loneliness are associated with an increased risk of individual CMD and CMM. In particular, loneliness acted as an independent risk factor in the transitions from healthy to CMD, ultimately to CMM (except from stroke to CMM). Considering the different aspects that contributed to the assessment of social isolation and loneliness, feeling lonely and living alone were more strongly associated with the risk of cardiometabolic outcomes than were having less social contact or social activities and less confiding to close people. Moreover, ideal healthy diet could attenuate the unfavorable association with cardiometabolic outcomes to some extent among the most isolated and the loneliest.

Stage I

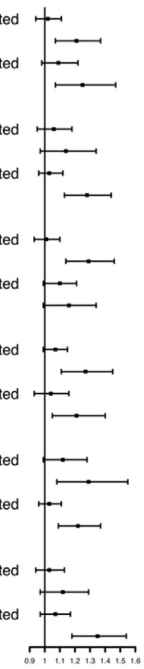
A

Subgroups		HR (95% CI)	P
Sex			**0.007**
Men	Moderately isolated	1.02 (0.99, 1.05)	
	Most isolated	1.04 (0.99, 1.09)	
Women	Moderately isolated	1.00 (0.97, 1.04)	
	Most isolated	1.11 (1.05, 1.17)	
Age			**0.001**
<60	Moderately isolated	1.04 (1.01, 1.08)	
	Most isolated	1.08 (1.02, 1,14)	
≥60	Moderately isolated	0.99 (0.96, 1.02)	
	Most isolated	1.06 (1.01, 1.12)	
BMI			**0.287**
<30	Moderately isolated	1.02 (0.99, 1.05)	
	Most isolated	1.05 (1.00, 1.10)	
≥30	Moderately isolated	1.01 (0.97, 1.05)	
	Most isolated	1.10 (1.03, 1.17)	
Townsend index			**0.114**
<0	Moderately isolated	1.01 (0.99, 1.04)	
	Most isolated	1.08 (1.03, 1.13)	
≥0	Moderately isolated	1.05 (1.00, 1.09)	
	Most isolated	1.09 (1.03, 1.15)	
Physical activity			**0.588**
Inactive	Moderately isolated	1.03 (0.98, 1.08)	
	Most isolated	1.10 (1.02, 1.18)	
Active	Moderately isolated	1.01 (0.99, 1.04)	
	Most isolated	1.06 (1.02, 1.11)	
Healthy diet			**0.028**
Ideal	Moderately isolated	0.99 (0.96, 1.03)	
	Most isolated	1.06 (1.01, 1.12)	
Poor	Moderately isolated	1.04 (1.01, 1.08)	
	Most isolated	1.09 (1.03, 1.15)	



B

Subgroups		HR (95% CI)	P
Sex			**0.279**
Men	Moderately isolated	1.02 (0.94, 1.11)	
	Most isolated	1.21 (1.07, 1.37)	
Women	Moderately isolated	1.09 (0.98, 1.22)	
	Most isolated	1.25 (1.07, 1.47)	
Age			**0.593**
<60	Moderately isolated	1.06 (0.95, 1.18)	
	Most isolated	1.14 (0.97, 1,34)	
≥60	Moderately isolated	1.03 (0.96, 1.12)	
	Most isolated	1.28 (1.13, 1.44)	
BMI			**0.105**
<30	Moderately isolated	1.01 (0.93, 1.10)	
	Most isolated	1.29 (1.14, 1.46)	
≥30	Moderately isolated	1.10 (0.99, 1.21)	
	Most isolated	1.16 (0.99, 1.34)	
Townsend index			**0.989**
<0	Moderately isolated	1.07 (0.99, 1.15)	
	Most isolated	1.27 (1.11, 1.45)	
≥0	Moderately isolated	1.04 (0.93, 1.16)	
	Most isolated	1.21 (1.05, 1.40)	
Physical activity			**0.362**
Inactive	Moderately isolated	1.12 (0.99, 1.28)	
	Most isolated	1.29 (1.08, 1.55)	
Active	Moderately isolated	1.03 (0.96, 1.11)	
	Most isolated	1.22 (1.09, 1.37)	
Healthy diet			**0.141**
Ideal	Moderately isolated	1.03 (0.94, 1.13)	
	Most isolated	1.12 (0.97, 1.29)	
Poor	Moderately isolated	1.07 (0.97, 1.17)	
	Most isolated	1.35 (1.18, 1.54)	



Stage II

C

Subgroups		HR (95% CI)	P
Sex			**0.953**
Men	Moderately isolated	1.07 (1.00, 1.13)	
	Most isolated	1.12 (1.02, 1.23)	
Women	Moderately isolated	1.08 (0.98, 1.19)	
	Most isolated	1.16 (1.01, 1.33)	
Age			**0.284**
<60	Moderately isolated	1.03 (0.93, 1.13)	
	Most isolated	1.13 (0.99, 1,29)	
≥60	Moderately isolated	1.09 (1.02, 1.15)	
	Most isolated	1.12 (1.01, 1.23)	
BMI			**0.539**
<30	Moderately isolated	1.10 (1.03, 1.18)	
	Most isolated	1.15 (1.03, 1.29)	
≥30	Moderately isolated	1.05 (0.97, 1.13)	
	Most isolated	1.13 (1.02, 1.26)	
Townsend index			**0.351**
<0	Moderately isolated	1.10 (1.03, 1.17)	
	Most isolated	1.12 (1.00, 1.25)	
≥0	Moderately isolated	1.04 (0.95, 1.13)	
	Most isolated	1.16 (1.04, 1.30)	
Physical activity			**0.692**
Inactive	Moderately isolated	1.07 (0.97, 1.18)	
	Most isolated	1.10 (0.96, 1.26)	
Active	Moderately isolated	1.07 (1.01, 1.14)	
	Most isolated	1.16 (1.06, 1.27)	
Healthy diet			**0.002**
Ideal	Moderately isolated	1.06 (0.99, 1.14)	
	Most isolated	1.00 (0.90, 1.12)	
Poor	Moderately isolated	1.08 (1.00, 1.17)	
	Most isolated	1.28 (1.15, 1.43)	

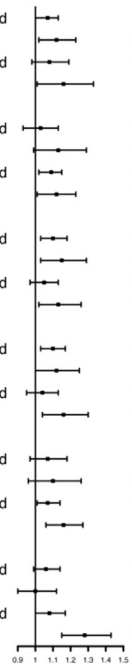


Figure 1. Associations between the three levels of social isolation and risks of CMD and CMM in Stage I and Stage II were stratified by sex, age, BMI, Townsend index, physical activity, and healthy diet

(A) Healthy to CMD; (B) Healthy to CMD; (C) CMD to CMM. The model was adjusted for age, sex, ethnicity and Townsend deprivation index, smoking status, alcohol consumption, physical activity, body mass index, healthy diet, education, income, antihypertensive drug use, lipid-lowering drug use, and aspirin use. CMD, cardiometabolic disease, CMM, cardiometabolic multimorbidity; HR, hazard ratio; CI, confidence interval; BMI, body mass index. Analysis of variance was used to test the interaction, and $p < 0.05$ was considered statistcally significant.

Comparison with other studies

To our knowledge, this is the first large-scale study on the impact of social isolation and loneliness on the transitions from CMD-free to FCMD, ultimately to CMM, and from single CMD to CMM. Only some cross-sectional and longitudinal studies have pointed to an association between multimorbidity and increased social exclusion as well as loneliness.[22,23] A population-based prospective cohort study reported that living alone was associated with a shorter leukocyte telomere length (LTL) and a higher risk of cardiovascular disease (CVD).[24] However, there is a lack of studies examining the effect of social isolation and loneliness on the incidence of multimorbidity in particular CMM. Our findings explored the promoting role of social isolation and loneliness in the development of CMM in healthy people and in patients with DM or CHD. Notably, loneliness seemed to have stronger effects on the transitions from CMD-free to CMM and from single CMD to CMM than social isolation. A more likely explanation is that these two factors measure different aspects of social relations and thus also have slightly different effect on health outcomes.[25–27]

The association of social isolation and loneliness with single CMD was inconclusive. Some studies demonstrated an independent unfavorable association between them, but others drew discrepant conclusions. A cohort study with 479,054 participants from the UK found that isolated and lonely persons were at increased risk of acute myocardial infarction and stroke, but most of this risk was explained by conventional risk factors.[28] Likewise, the associations of social isolation and loneliness with cardiovascular diseases and DM were fully explained by baseline psychological and behavioral factors in a cohort study of 24,687 individuals from Denmark.[29] Several studies revealed that loneliness, but not social isolation, was independently associated with CHDs onset,[30,31] but a systematic review and meta-analysis revealed an unfavorable correlation between social isolation and CHDs,[32] and in a cohort study from the US, social isolation was also independently associated with modestly higher risk of CHDs among postmenopausal women, and those with both social isolation and loneliness had greater cardiovascular disease risk than did those with either exposure alone.[20] Here, the findings of our analysis were partly consistent with the previous prospective studies that serial adjustment indeed led to attenuation of the association of social isolation with increased risk of CHD, but not that with stroke or DM. In contrast, loneliness was an independent risk factor for any kind of the three CMDs. The differences in findings could be related to study design or methodological issues. Besides, it was possible that some adjustment for confounding factors lead to an underestimation of the true effect. In addition, we found that healthy women were more prone to developing single CMD than men, which was consistent with previous findings.[33,34]

Implications

Limited interventions have demonstrated long-term effectiveness in reducing loneliness in adults with chronic conditions.[35] O'Keefe et al. found that plants and pets were potent allies in the struggle against loneliness, especially for people living alone during the COVID-19

Table 3. Associations between the three levels of loneliness and different cardiometabolic endpoints in Stage I and Stage II

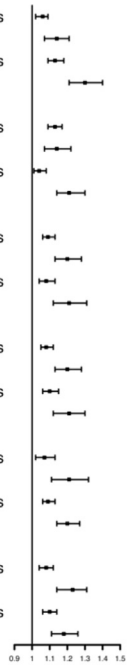
		Model 1		Model 2		Model 3	
Variable		HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Stage I	**Healthy to CMD (n = 34,589)**						
	Least loneliness	1.00		1.00		1.00	
	Moderately loneliness	1.20 (1.17, 1.23)	<0.001	1.13 (1.10, 1.15)	<0.001	1.09 (1.06, 1.12)	<0.001
	Most loneliness	1.44 (1.38, 1.51)	<0.001	1.27 (1.21, 1.33)	<0.001	1.20 (1.15, 1.26)	<0.001
	Healthy to CMM (n = 4,474)						
	Least loneliness	1.00		1.00		1.00	
	Moderately loneliness	1.41 (1.32, 1.51)	<0.001	1.27 (1.19, 1.36)	<0.001	1.20 (1.12, 1.28)	<0.001
	Most loneliness	1.75 (1.55, 1.98)	<0.001	1.42 (1.26, 1.61)	<0.001	1.29 (1.14, 1.46)	<0.001
Stage II	**CMD to CMM (n = 6,981)**						
	Least loneliness	1.00		1.00		1.00	
	Moderately loneliness	1.19 (1.13, 1.25)	<0.001	1.13 (1.07, 1.19)	<0.001	1.09 (1.04, 1.15)	0.001
	Most loneliness	1.52 (1.40, 1.65)	<0.001	1.37 (1.26, 1.49)	<0.001	1.30 (1.19, 1.42)	<0.001

Model 1 was adjusted for age, sex and ethnicity.
Model 2 was additionally adjusted for BMI, smoking status, alcohol consumption, physical activity, and healthy diet.
Model 3 was further adjusted for Townsend deprivation index, education, income, antihypertensive drug use, lipid-lowering drug use, and aspirin use.
CMD, Cardiometabolic diseases; CMM, Cardiometabolic Multimorbidity; HR, hazard ratio; CI, confidence interval.

Stage I

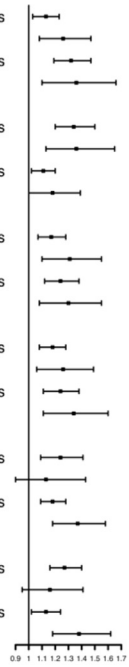
A

Subgroups		HR (95% CI)	P
Sex			**<0.001**
Men	Moderately loneliness	1.06 (1.02, 1.09)	
	Most loneliness	1.14 (1.07, 1.21)	
Women	Moderately loneliness	1.13 (1.09, 1.18)	
	Most loneliness	1.30 (1.21, 1.40)	
Age			**<0.001**
<60	Moderately loneliness	1.13 (1.09, 1.17)	
	Most loneliness	1.14 (1.07, 1,22)	
≥60	Moderately loneliness	1.04 (1.01, 1.08)	
	Most loneliness	1.21 (1.14, 1.30)	
BMI			**0.766**
<30	Moderately loneliness	1.09 (1.06, 1.13)	
	Most loneliness	1.20 (1.13, 1.28)	
≥30	Moderately loneliness	1.08 (1.04, 1.13)	
	Most loneliness	1.21 (1.12, 1.31)	
Townsend index			**0.209**
<0	Moderately loneliness	1.08 (1.05, 1.12)	
	Most loneliness	1.20 (1.13, 1.28)	
≥0	Moderately loneliness	1.10 (1.06, 1.15)	
	Most loneliness	1.21 (1.12, 1.30)	
Physical activity			**0.761**
Inactive	Moderately loneliness	1.07 (1.02, 1.13)	
	Most loneliness	1.21 (1.11, 1.32)	
Active	Moderately loneliness	1.09 (1.06, 1.13)	
	Most loneliness	1.20 (1.14, 1.27)	
Healthy diet			**0.470**
Ideal	Moderately loneliness	1.08 (1.04, 1.12)	
	Most loneliness	1.23 (1.14, 1.31)	
Poor	Moderately loneliness	1.10 (1.06, 1.14)	
	Most loneliness	1.18 (1.11, 1.26)	



B

Subgroups		HR (95% CI)	P
Sex			**0.050**
Men	Moderately loneliness	1.13 (1.03, 1.23)	
	Most loneliness	1.26 (1.08, 1.47)	
Women	Moderately loneliness	1.32 (1.19, 1.47)	
	Most loneliness	1.36 (1.10, 1.66)	
Age			**0.001**
<60	Moderately loneliness	1.34 (1.20, 1.50)	
	Most loneliness	1.36 (1.13, 1,65)	
≥60	Moderately loneliness	1.11 (1.02, 1.20)	
	Most loneliness	1.18 (1.00, 1.39)	
BMI			**0.760**
<30	Moderately loneliness	1.17 (1.07, 1.28)	
	Most loneliness	1.31 (1.10, 1.55)	
≥30	Moderately loneliness	1.24 (1.12, 1.38)	
	Most loneliness	1.30 (1.08, 1.55)	
Townsend index			**0.620**
<0	Moderately loneliness	1.18 (1.08, 1.28)	
	Most loneliness	1.26 (1.06, 1.49)	
≥0	Moderately loneliness	1.24 (1.11, 1.38)	
	Most loneliness	1.34 (1.11, 1.60)	
Physical activity			**0.236**
Inactive	Moderately loneliness	1.24 (1.09, 1.41)	
	Most loneliness	1.13 (0.90, 1.43)	
Active	Moderately loneliness	1.18 (1.09, 1.28)	
	Most loneliness	1.37 (1.18, 1.58)	
Healthy diet			**0.049**
Ideal	Moderately loneliness	1.27 (1.16, 1.40)	
	Most loneliness	1.16 (0.95, 1.41)	
Poor	Moderately loneliness	1.13 (1.02, 1.24)	
	Most loneliness	1.38 (1.18, 1.62)	



Stage II

C

Subgroups		HR (95% CI)	P
Sex			**0.898**
Men	Moderately loneliness	1.09 (1.02, 1.16)	
	Most loneliness	1.30 (1.18, 1.45)	
Women	Moderately loneliness	1.12 (1.02, 1.23)	
	Most loneliness	1.29 (1.10, 1.51)	
Age			**0.041**
<60	Moderately loneliness	1.18 (1.07, 1.30)	
	Most loneliness	1.27 (1.10, 1.46)	
≥60	Moderately loneliness	1.05 (0.98, 1.12)	
	Most loneliness	1.27 (1.14, 1.42)	
BMI			**0.39(**
<30	Moderately loneliness	1.07 (0.99, 1.15)	
	Most loneliness	1.24 (1.09, 1.41)	
≥30	Moderately loneliness	1.14 (1.06, 1.23)	
	Most loneliness	1.37 (1.22, 1.54)	
Townsend index			**0.339**
<0	Moderately loneliness	1.08 (1.01, 1.16)	
	Most loneliness	1.25 (1.11, 1.41)	
≥0	Moderately loneliness	1.12 (1.02, 1.22)	
	Most loneliness	1.35 (1.19, 1.53)	
Physical activity			**0.161**
Inactive	Moderately loneliness	1.19 (1.08, 1.31)	
	Most loneliness	1.28 (1.10, 1.50)	
Active	Moderately loneliness	1.06 (0.99, 1.13)	
	Most loneliness	1.31 (1.18, 1.46)	
Healthy diet			**0.005**
Ideal	Moderately loneliness	1.02 (0.95, 1.10)	
	Most loneliness	1.19 (1.04, 1.35)	
Poor	Moderately loneliness	1.19 (1.10, 1.28)	
	Most loneliness	1.40 (1.25, 1.58)	

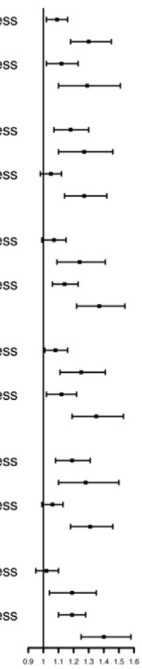


Figure 2. Associations between the three levels of loneliness and risks of CMD and CMM in Stage I and Stage II were stratified by sex, age, BMI, Townsend index, physical activity, and healthy diet

(A) Healthy to CMD; (B) Healthy to CMD; (C) CMD to CMM. The model was adjusted for age, sex, ethnicity and Townsend deprivation index, smoking status, alcohol consumption, physical activity, body mass index, healthy diet, education, income, antihypertensive drug use, lipid-lowering drug use, and aspirin use. CMD, cardiometabolic disease; CMM, cardiometabolic multimorbidity; HR, hazard ratio; CI, confidence interval; BMI, body mass index.

pandemic.[36] Dogs compel their owners to higher levels of physical activity (PA), exercise, and fitness, and reduce psychosocial stress (PSS) levels.[37] People living alone with a dog have a 33% lower risk of all-cause mortality and a 36% lower risk of CVD mortality compared with those without a dog.[38] Moreover, social isolation is a modifiable determinant. In the COVID-19 era, information and communication technology (ICT) such as smart homes can help detect and predict loneliness and social isolation, and technologies such as robotic pets and some other social robots can help alleviate loneliness to some extent.[39] Our study provides further motivation to positive social interactions in order to attenuate the adverse effects of social isolation on incident CMD and CMM. Moreover, given that poor diet played a critical role in the development of CMDs among the isolated and lonely people, ideal dietary advice should be promoted, particularly in people who live alone and feel lonely. Similarly, consideration should be given to randomized trials to investigate the effect of government interventions on the improvement of adverse cardiometabolic outcomes for isolated and lonely people.

Strengths of the study

One of the important strengths of this study is that we assessed more than one type of social relationship (from objective and subjective, physical and mental), which might better provide information for formulating precise preventive strategies. Besides, a multi-item assessment of social isolation and loneliness also had the best predictive validity for cardiometabolic outcomes. Another strength is that we explored associations of social isolation and loneliness with different stages of diseases, such as from CMD-free to FCMD to CMM, and from single CMD to CMM. The influence of confounding was attenuated by statistical adjustment for a wide range of covariates and through a series of sensitivity analyses. Otherwise, the large sample from UK Biobank also allowed us to perform the analyses with sufficient statistical power and reduced risk of random error. Other strengths of this study include the prospective design, a follow-up period more than a decade and inosculating the current COVID-19 epidemic background.

Limitations of the study

Nevertheless, this study also has limitations. First, isolated participants might have the feeling of loneliness, and the converse held true as well. Though the interaction between loneliness and social isolation was not significant,[29] we did not account for the synergistic effect of the co-occurrence of social isolation and loneliness on the associations with CMD and CMM, even if this relatively small overlying would likely have little effect on our main findings. Second, there is still a possibility of residual confounding that cannot be completely ruled out in an observational study, and causation cannot be tested. Also, absolute risks from this study might not be estimated even though the individual characteristics of the cohort and statistic validity are similar to those studies conducted in the general population.[40,41] Finally, information on social isolation and loneliness was mainly self-reported and was only measured once, thus measurement errors were inevitable, particularly in the multistate model analyses.

Conclusions

Based on a large UK prospective cohort, social isolation and loneliness were found to be significantly associated with higher risk of incident CMM in people with or without single CMD, which disclosed the importance of acknowledging social isolation and loneliness as additional behavioral and psychosocial risk factors for cardiometabolic diseases. In the context of the COVID-19 pandemic, identifying high-risk populations through the levels of social isolation and loneliness and adopting social prescribing that links primary care with community resources may help to attenuate the progression of CMM. Health policies improving the state of living alone and feeling lonely and referring individuals at high risk of CHD to social contact might be applicable for the precise prevention and treatment of CMDs. Moreover, ideal dietary advice might substantially reduce the incidence of CMD and CMM among the most isolated and the loneliest.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.109109.

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AUTHOR CONTRIBUTIONS

Z.L.X. and J.L. contributed equally to this work and are joint first authors. Y.P.B. designed the study. X.J.C. designed data collection tools, monitored data collection for the whole trial, wrote the statistical analysis plan. J.L. conducted the data analysis and revised the manuscript. Z.L.X. drafted and revised the manuscript. Y.L. and L.Y. acquired and interpreted the data, and critically revised the manuscript for important content. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare that they have no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
R Version 4.1.1	R Foundation	https://www.r-project.org/

RESOURCE AVAILABILITY

Lead contact

Further information should be directed to and will be fulfilled by the lead contact, Yongping Bai (baiyongping@csu.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The UK Biobank dataset was downloaded from https://www.ukbiobank.ac.uk.
- All original code in the paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Ethics approval and consent to participate

Ethics approval for the UK Biobank study was obtained from the North West Centre for Research Ethics Committee (11/NW/0382). All participants provided written informed consent.

METHOD DETAILS

Study design and participants

The UK Biobank project is a prospective cohort study of approximately 500,000 individuals from across the United Kingdom, aged between 37 and 73 years recruited in 2006-2010.[4,28] At recruitment, all participants provided electronic signed consent, completed a touch screen questionnaire that collected information on socio- demographic, lifestyle and health-related factors. Besides, questions on social contact were the baseline for our analyses. Follow-up information was provided by linking health and medical records, and participants were tracked for morbidity and mortality.[42] The UK Biobank received the ethical approval from the North West Multi-Centre Research Ethics Committee, and electronic consent was provided by all participants for the assessments at baseline and follow-ups.

In the present study, we excluded participants with any of the following: (1) with CMM at baseline; (2) with incomplete data on either social isolation or loneliness, CMD and CMM; (3) with missing data for confounding variables. Finally, a total of 378,669 participants were eligible for subsequent analyses, including 343,425 individuals with no CMD at baseline and 35,209 individuals with one CMD at baseline (Figure S1).

Assessment of variables

Social isolation and loneliness are related but conceptually different constructs: the former refers to objective lack of social interactions and small size of social network behaviourally, while the latter refers to perceived social isolation or subjective mental distress due to unsatisfaction with the quality and quantity of social relationship.[43,44] Social isolation and loneliness were assessed with scales[45] constructed from the questionnaires in UK Biobank.[46] The scale for social isolation contained three questions: (1) "Including yourself, how many people are living together in your household?"; (2) "How often do you visit friends or family or have them visit you?"; and (3) "Which of the following (sports club or gym, pub or social club, religious group, adult education class, other group activity) do you engage in once a week or more often?". High-risk factors of social isolation included living alone; less social contact (friends and family visits less than monthly); and less social activities (less than weekly or never). According to the answers, 1 point was given for one high-risk factor, and 0 point was given for none. Thus, individuals could score ranging from 0 to 3, and those who scored 0 were defined as least isolated, who scored 1 were defined as moderately isolated, and who scored 2 or 3 were defined as most isolated since few individuals had scores of 3. Loneliness was assessed with two questions: "Do you often feel lonely?" and "How often are you able to confide in someone close to you?". High-risk factors of loneliness included feeling lonely and less confiding in close people (never or almost never). For each loneliness behavior, individual received 1 point if meeting the high-risk factor and 0 point if not. All factor scores were summed to obtain a loneliness score ranging from 0 to 2. An individual was defined as least loneliness if he or she scored 0, moderately loneliness if he or she scored 1, and most loneliness if he or she scored 2.

Covariates incorporated: (1) sociodemographics (i.e., age, gender and ethnicity); (2) biological (i.e., body mass index); (3) behavioural (i.e., smoking, alcohol consumption, healthy diet, and physical activity); (4) socioeconomic (i.e., Townsend deprivation index, educational attainment and household income); (5) chronic conditions related (i.e., antithrombotic or antihypertensive or lipid-lowering drug use, and depression). Detailed descriptions of the covariates have been provided in Table S1.

Outcome ascertainment

The primary outcomes in the present study were cardiometabolic disease and cardiometabolic multimorbidity. Cardiometabolic multimorbidity is defined as the coexistence of two or three cardiometabolic diseases, including diabetes mellitus, coronary heart disease, and stroke. Details descriptions of the diseases[47] can be found in Table S2. The survival time for participants was from the date of enrollment to the date of occurrence of the outcomes, or the last known follow-up (June, 2021), whichever came first. In participants who did not have a diagnosis of any cardiometabolic disease at baseline (stage I), the data of diagnosis of the first cardiometabolic disease without progression to the next cardiometabolic disease, was considered the time of CMD; the date of diagnosis of the second cardiometabolic disease was considered the time of CMM. In participants who already had a diagnosis of one cardiometabolic disease at baseline (stage II), the date of diagnosis of the second cardiometabolic disease was considered the time of CMM.

Statistical analysis

For baseline characteristics comparisons grouped by outcome, we performed Student's *t*-tests for the analysis of continuous data (expressed as mean $\pm$ SD) and χ^2 test for the analysis of categorical variables (expressed as percentage). In survival analysis, Kaplan–Meier curves were applied to show differences in survival time according to the three levels of social isolation and loneliness. Cox proportional hazards models were used to model the association between social isolation/loneliness and the incidence of CMD and CMM by calculating the hazard ratios (HR) and corresponding 95% confidence intervals (95% CIs). Three models were fitted: model 1 was adjusted for age, sex and ethnicity; model 2 was adjusted for model 1 plus BMI, frequency of alcohol intake, smoking status, physical activity, ideal healthy diet; model 3 (fully adjusted) was adjusted for model 2 plus medications for lipid lowering, Aspirin, medications for antihypertension, education, income and Townsend deprivation index. The least isolated/loneliness group was the reference category.

To identify a group of individuals who are associated with higher risk of CMD and CMM, we performed exploratory subgroup analysis by age, sex, and Townsend index. We further sought to explore some modifiable factors and find out the potential intervention strategies, we conducted exploratory subgroup analysis according to BMI, physical activity, and healthy diet.

Four sensitivity analyses were conducted to enhance the reliability of our results. First, to investigate whether the associations of social isolation and loneliness with cardiometabolic outcomes are independent from each other, we additionally adjusted for the other factor. Second, we additionally adjusted for depression, which could represent either a potential confounder.[19] Third, we excluded individuals diagnosed with cardiometabolic diseases that occurred within 2 years after recruitment to minimize reverse causality of social isolation and loneliness with cardiometabolic outcomes. Lastly, we further used a multi-state model (MSM) to explore the impacts of social isolation and loneliness on each transitional stage of CMM progression (i.e., from CMD-free to single CMD, and then to CMM).

All statistical analyses were performed using R software (version 4.1.1). A two-sided *P*-value < 0.05 was considered statistically significant.