

Supplement

Title: Social isolation, loneliness, and subsequent risk for major adverse cardiovascular events among individuals with type 2 diabetes mellitus

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Supplemental Methods:

eText 1. Detailed information on inclusion and exclusion of this study

The present study included individuals with type 2 diabetes mellitus (T2DM) at baseline that was confirmed by integrating multiple data sources.[1] First, we identified the presence of T2DM using a validated algorithm integrating data regarding self-reported disease, medications, and medical history.[2] The UK Biobank team collected data through a touchscreen questionnaire and verbal interviews by a trained nurse at baseline. Second, participants with an HbA1c level $\geq 6.5\%$ (≥ 48 mmol/mol)[3] were considered as having prevalent diabetes mellitus. Subsequently, we excluded participants with probable type 1 diabetes mellitus or gestational diabetes mellitus, which were ascertained by using the algorithm mentioned above.[2] We excluded participants who did not respond to online survey assessing social isolation or loneliness and those who had invalid data of exposures (respond “prefer not to answer” or “don’t know” to the questionnaires). Next, those with existing ischaemic heart disease (including myocardial infarction), stroke, or cancer at baseline were also excluded. Thus, 19 360 participants with T2DM were included in the main analysis.

eText 2. Assessment of social isolation and loneliness in the UK Biobank

At baseline, social isolation and loneliness were assessed with a touchscreen questionnaire using five questions, which are listed Supplemental in the UK Biobank. (<https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=446>).

Social isolation was assessed with the following three questions:

Subitem 1: Live alone:

a) “Including yourself, how many people are living together in your household?” (1 point was given for living alone; field ID: 709);

Subitem 2: Contact with family/friends or groups:

b) “How often do you visit friends or family or have them visit you?” (1 point was given for answering about once a month, once every few months, never or almost never, or no friends or family outside the household; field ID: 1031);

c) “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?” (1 point was given for answering none of the above; field ID: 6160).

Thus, individuals could score a total of 0-3. Individuals were defined as least isolated if they scored 0, moderately isolated if they scored 1, and most isolated if they scored 2 or 3. Individuals were defined little contact with family/friends or groups when they scored 1 or 2 on the two questions about the family or friends and about groups. Similar scales have been used previously in other UK studies.

Loneliness was assessed with two questions:

Subitem 1: Lonely:

a) “Do you often feel lonely?” (1 point was given for answering yes; field ID: 2020);

Subitem 2: Able to confide:

b) “How often are you able to confide in someone close to you?” (1 point was given for answering never or almost never; field ID: 2110).

The individual was defined as lonely if they scored 2. Similar questions are included in scales such as the revised UCLA Loneliness Scale.

eText 3. Assessment of potential covariates and mediators in the UK Biobank

We used the self-reported questionnaires, physical-measured variables, and medical history to assess the confounders. Age (continuous, calculated from dates of birth; field ID 21003), sex (Female, Male; field ID 31), assessment centre (England, Scotland, Wales; field ID 54), and Townsend Deprivation Index (continuous; a

higher score indicates a higher degree of deprivation which was based on postcode; field ID 189) were known before arrival at the Assessment Centre.

The following covariate data were obtained from touchscreen questions or verbal interview at baseline: ethnicity (White, Others; field ID 21000), current employment status (employed, unemployed; field ID 6142), education level (college or university degree, non-college or university degree; field ID 6138), smoking status (never, current, past; field ID 20116), alcohol consumption status (not current, less than three times a week, three or more times a week; field ID 1558), physical activity (continuous, MET, metabolic equivalent task-summed days; field ID 22033), TV watching time (continuous, hours, day; field ID 1070), healthy diet score (continuous, 0-5 points; field ID 1289, 1299, 1309, 1319, 1329, 1339, 1369, 1379, 1389, and 1349), self-reported sleep duration (short: <7 hours/day, normal: 7 to 8 hours/day, and long: >8 hours/day; field ID 1160), ever seeking help from physicians due to anxiety or depressive symptoms (yes/no; field ID 2100 and 2090), family history of diabetes (yes/no; field ID 20107 and 20110), and diabetes medication use (oral antidiabetic drug only/insulin/ neither, field ID 20003, 6153 and 6177).

The healthy diet score was calculated by using the following dietary factors: vegetable intake at least four tablespoons each day (median); fruits intake at least three pieces each day (median); fish intake at least twice each week (median); unprocessed red meat intake no more than twice each week (median); and processed meat intake no more than two each week (median). Each one point was given for each favourable diet factor, with the total diet score ranging from 0 to 5.

Obesity status (underweight or normal-weight, overweight, obese; field ID 21001), grip strength (continuous; field ID 46 and 47), systolic blood pressure (continuous, mmHg, field ID 4080 and 93), diastolic blood pressure (continuous, mmHg, field ID 4079 and 94) were collected by physical measurements. HbA1c (<53 or \geq 53 mmol/mol, 7%; according to ADA guideline; field ID 30750) was measured with high-performance liquid chromatography analysis on a Bio-Rad VARIANT II TURBO analyser. Diabetes duration (ICD: E110-E119), obtained from self-reported data or the hospital records and death registries, was calculated as the years between first onset of diabetes and baseline for diagnosed patients, while diabetes duration was assigned as 0 years for those undiagnosed patients[4]. Estimated glomerular filtration rate (continuous, mL/min, field ID 21003, 31, 21000, 30700) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation[5]. Anxiety (ICD: F40-F41) and depression (ICD: F32 [single episode depression], F33 [recurrent depression], F34 [persistent mood disorders], F38 [other mood disorders], and F39 [unspecified mood disorders]) were obtained through hospital inpatient records. Information on prevalent diseases (hyperlipidaemia, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, osteoarthritis) was obtained through self-reported and hospital inpatient records (eTable 1).

We constructed two regression models: a Cox proportional hazard model to regress the outcome on the exposure and the mediator, and a linear model to regress the mediator on the exposure. The two regression models were adjusted for age, sex, ethnicity, assessment centres, employment status, education, and Townsend Deprivation Index. We used regression-based approaches[6] to estimate the total effect, total natural indirect effect (TNIE), and total natural direct effect (TNDE). The TNDE presents the effect of the exposure (social isolation/loneliness) on the outcome that was independent of the mediators. The TNIE presents the proportion of exposure that could be explained by its association with the mediators. To quantify the magnitude of mediation, the proportion of mediating effect was estimated by the mediator (TNIE/[TNDE + TNIE]). We used bootstrapping (1000 replications) to obtain the correct 95% CIs.

eText 4. Imputation procedure

We used the "mice" package (v3.13.0) in R to conduct multiple imputations for missing values. [eTable 2](#) provides detailed information on the numbers (percentages) and patterns of missing data for the covariates, which were imputed in the main analyses. For the sensitivity analysis wherein the invalid values of social isolation or loneliness were imputed, we included the participants who gave responses of 'prefer not to answer' or 'don't know' (which were defined as invalid data). To conduct the multiple imputation for both main and sensitivity analyses, following Sterne et al.'s recommendations (3), we included the exposures, covariates, disease and mortality outcomes, and time to these outcomes as predictors in the imputation models. We generated 20 imputed datasets with a maximum of 20 iterations to impute missing values using Rubin's rules to estimate the effects.

References

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eTable 1. Information about exposures, outcomes, covariates, and mediators

Variables	Field ID/ ICD-10 codes
Exposures	
Social isolation	Field ID 709/1031/6160
Loneliness	Field ID 2020/2110
Outcomes	
All-cause mortality	ICD A00-U89
CVD cause mortality	ICD I00-I99
Myocardial infarction	ICD I21/I22/I23/I24.1/I25.2
Stroke	ICD I60–I64, I69
Potential covariates and mediators	
Age (continuous, years)	Field ID 21003
Sex (male/female)	Field ID 31
Ethnicity (White/others)	Field ID 21000
Assessment centre (England/Scotland/Wales)	Field ID 54
Current employment status (employed/unemployed)	Field ID 6142
Education level (college or university degree/non-college or university degree)	Field ID 6138
Townsend Deprivation Index (continuous, a higher score indicates a higher degree of deprivation)	Field ID 189
Smoking status (never/current/past)	Field ID 20116
Alcohol consumption status (not current/less than three times a week/three or more times a week)	Field ID 1558
Physical activity (MET Score) (continuous, metabolic equivalent task-summed days)	Field ID 22033
TV watching time (continuous, hours/day)	Field ID 1070
Healthy diet score (continuous, 0–5 points)	Field ID 1289/1299/1309/1319/1329/1339/1349/1369/1379/1389
Sleep duration (short: ≤ 6 hours/day, normal: 7–8 hours/day, long: ≥ 9 hours/day)	Field ID 1160
Anxiety	ICD F40-F41
Depression	ICD F32/F33/F34/F38/F39
Ever seeking help from physicians due to anxiety or depressive symptoms (yes/no)	Field ID 2100 and 2090
Obesity status (grouped using body mass index, underweight or normal weight/overweight/obese)	Field ID 21001
Grip strength (continuous, kg)	Field ID 46/47
Systolic blood pressure (continuous, mmHg)	Field ID 4080/93
Diastolic blood pressure (continuous, mmHg)	Field ID 4079/94
Hyperlipidaemia (yes/no)	Field ID 20002/6153/6177

	ICD E78
Family history of diabetes (yes/no)	Field ID 20107/20110
HbA1c (continuous, mmol/mol)	Field ID 30750
Diabetes duration (continuous)	ICD E110-E119
Diabetes medication use (oral antidiabetic drug only/insulin/ neither)	Field ID 20003/6153/6177
Estimated glomerular filtration rate (continuous, mL/min)	Filed ID 21003/31/21000/30700
Chronic kidney disease (yes/no)	ICD I12, I12.0, I12.9, I13.1, I13.2, I13.9, N02, N03, N04, N05, N06, N07, N08.0-08.5, N08.8, N11, N11.0, N11.1, N11.8, N11.9, N16.5, N17.0-17.2, N17.8-17.9, N18.0-18.5, N18.8, N18.9, N19, N25.0, N26, N27, N27.0, N27.1, N27.9, N28.0, N39.1, Q60, Q60.0-60.6, Q61.1-61.5, Q63, Q63.0-63.3, Q63.8, Q63.9, R80, R94.4, T86.1, Z49, Z49.0-49.2, Z841, Z94.0, Z99.2, Z92.2
Diabetes-related microvascular disease (yes/no)	ICD E113, E143, H280, H360, E114, E144, G730, G990, G590, G632, E116, E146
Neurodegenerative disease (yes/no)	Field ID 20002 ICD F01-03, G122, G20, G21, G231-233, G238, G239, G30, G31
Respiratory disease (yes/no)	Field ID 20002/6152 ICD J40-J44, J47
Digestive disease (yes/no)	Field ID 20002 ICD K70-K77
Rheumatoid arthritis (yes/no)	Field ID 20002 ICD M199
Osteoarthritis (yes/no)	Field ID 20002/6152 ICD M05-M06

MET, metabolic equivalent of task; ICD-10 codes, International Classification of Diseases, Tenth Revision.

Supplemental Results:**eTable 2. The number (percentage) of participants with missing covariate data in the analytic sample**

Covariates	N	%
Age	0	0.00
Sex	0	0.00
Ethnicity	71	0.37
Assessment centre	0	0.00
Current employment status	161	0.83
Education level	265	1.37
Townsend Deprivation Index	31	0.16
Smoking status	106	0.55
Alcohol consumption status	15	0.08
Physical activity (MET Score)	3563	18.40
TV watching time	224	1.16
Healthy diet score	3	0.02
Sleep duration	175	0.90
Ever seeking help from physicians due to anxiety or depressive symptoms	150	0.77
Obesity status	154	0.80
Grip strength	152	0.79
Systolic blood pressure	51	0.26
Diastolic blood pressure	50	0.26
Hyperlipidaemia	0	0.00
Family history of diabetes	858	4.43
HbA1c	1205	6.22
Diabetes duration	1208	6.24
Diabetes medication use	1080	5.58
Estimated glomerular filtration rate	1178	6.08
Chronic kidney disease	0	0.00
Diabetes-related microvascular disease	0	0.00
Neurodegenerative disease	569	2.94
Respiratory disease	569	2.94
Digestive disease	569	2.94
Rheumatoid arthritis	0	0.00
Osteoarthritis	569	2.94

MET, metabolic equivalent of task.

eTable 3. Comparison of baseline characteristics between the total sample of the UK Biobank and the participants included in the present analysis

Characteristics	Total (N = 502,505)	Excluded (N = 483,145)	Included (N = 19,360)
Age, mean (SD), yrs	56.5 (8.1)	56.4 (8.1)	59.4 (7.0)
Sex, male (%)	229,122 (45.6)	217,302 (45.0)	11,820 (61.1)
Ethnicity, White (%)	472,695 (94.1)	455,700 (94.3)	16,995 (87.8)
Assessment centre (%)			
England	445,855 (88.7)	428,618 (88.7)	17,237 (89.0)
Scotland	35,841 (7.1)	34,608 (7.2)	1233 (6.4)
Wales	20,808 (4.1)	19,918 (4.1)	890 (4.6)
Currently employed (%)	287,149 (57.1)	278,679 (57.7)	8470 (43.8)
College or university degree (%)	161,163 (32.1)	156,449 (32.4)	4714 (24.3)
Townsend Deprivation Index*	-1.3 (3.1)	-1.3 (3.1)	-0.5 (3.4)
Current smokers (%)	52,978 (10.5)	50,768 (10.5)	2210 (11.4)
Alcohol consumption status (%)			
Not current	40,635 (8.1)	37,773 (7.8)	2862 (14.8)
Less than three times a week	243,131 (48.4)	232,595 (48.1)	10,536 (54.4)
Three or more times a week	217,194 (43.2)	211,247 (43.7)	5947 (30.7)
Physical activity (MET Score), mean (SD)	10.6 (4.8)	10.7 (4.8)	9.7 (5.0)
TV watching time (hours/day), mean (SD)	2.8 (1.7)	2.8 (1.7)	3.4 (2.0)
Healthy diet score, median [IQR]	3 [2-4]	3 [2-4]	3 [2-4]
Sleep duration (%)			
Short (<7 hours/day)	123,252 (24.5)	117,870 (24.4)	5382 (27.8)
Normal (7-8 hours/day)	340,906 (67.8)	329,187 (68.1)	11,719 (60.5)
Long (>8 hours/day)	38,347 (7.6)	36,088 (7.5)	2259 (11.7)
Anxiety (%)	1750 (0.3)	1661 (0.3)	89 (0.5)
Depression (%)	4765 (0.9)	4469 (0.9)	296 (1.5)
Ever seeking help from physicians due to anxiety or depressive symptoms (%)	173,164 (34.5)	166,422 (34.4)	6742 (34.8)
Obesity status (kg/m ²)			
Underweight or normal weight (%)	165,020 (32.8)	163,139 (33.8)	1881 (9.7)
Overweight (%)	212,098 (42.2)	205,599 (42.6)	6499 (33.6)
Obese (%)	122,238 (24.3)	111,412 (23.1)	10,826 (55.9)
Grip strength (kg), mean (SD)	30.6 (11.0)	30.6 (11.0)	30.6 (11.1)

Systolic blood pressure (mmHg), mean (SD)	140 (20)	140 (20)	145 (18)
Diastolic blood pressure (mmHg), mean (SD)	82 (11)	82 (11)	83 (10)
Hyperlipidaemia (%)	94,027 (18.7)	80,762 (16.7)	13,265 (68.5)
Estimated glomerular filtration rate, mean (SD), mL/min/1.73 m ²	90.8 (13.4)	90.8 (13.3)	89.9 (15.6)
Family history of diabetes (%)	85,798 (17.1)	79,052 (16.4)	6746 (34.8)
HbA1c, median [IQR], %	5.4 [5.2-5.6]	5.4 [5.1-5.6]	6.8 [6.2-7.5]
Diabetes duration, median [IQR], yrs	1.0 [0.0-6.0]	-	4.0 [1.0-8.0]
Diabetes medication use (%)			
Neither	344,899 (68.6)	338,282 (70.0)	6617 (34.2)
Oral antidiabetic drug only	13,404 (2.7)	4181 (0.9)	9223 (47.6)
Insulin	5695 (1.1)	3255 (0.7)	2440 (12.6)
Chronic kidney disease (%)	3618 (0.7)	3 290 (0.7)	328 (1.7)
Diabetes-related microvascular disease (%)	1008 (0.2)	687 (0.1)	321 (1.7)
Neurodegenerative disease (%)	1320 (0.3)	1270 (0.3)	50 (0.3)
Respiratory disease (%)	11,426 (2.3)	10,709 (2.2)	717 (3.7)
Digestive disease (%)	2291 (0.5)	2030 (0.4)	261 (1.3)
Rheumatoid arthritis (%)	5658 (1.1)	5348 (1.1)	310 (1.6)
Osteoarthritis (%)	40,684 (8.1)	38,586 (8.0)	2098 (10.8)

*Positive values of the index will indicate areas with high material deprivation, whereas those with negative values will indicate relative affluence.

IQR, interquartile range; MET, metabolic equivalent of task; SD, standard deviation.

eTable 4. Associations of social isolation with subsequent risk for mortality, myocardial infarction, and stroke in patients with type 2 diabetes mellitus

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Social isolation					
	Moderately vs. least	8147	12.2	1.28 (1.17-1.39)	1.18 (1.08-1.28)	1.16 (1.06-1.27)
	Most vs. least	3804	15.4	1.70 (1.54-1.88)	1.36 (1.22-1.51)	1.33 (1.19-1.47)
	Items					
	Contacts (little vs. more)	9601	12.9	1.25 (1.16-1.35)	1.13 (1.04-1.22)	1.10 (1.02-1.19)
	Live alone (yes vs. no)	4602	16.3	1.55 (1.43-1.68)	1.30 (1.20-1.42)	1.31 (1.20-1.42)
CVD mortality	Social isolation					
	Moderately vs. least	8147	6.1	1.39 (1.23-1.57)	1.25 (1.10-1.42)	1.22 (1.08-1.39)
	Most vs. least	3804	7.7	1.85 (1.61-2.13)	1.41 (1.21-1.64)	1.36 (1.17-1.59)
	Items					
	Contacts (little vs. more)	9601	6.5	1.33 (1.20-1.48)	1.16 (1.04-1.30)	1.13 (1.01-1.26)
	Live alone (yes vs. no)	4602	8.2	1.65 (1.47-1.84)	1.36 (1.21-1.54)	1.37 (1.22-1.55)
Overall						
Composites of incident myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8147	10.1	1.12 (1.02-1.23)	1.02 (0.93-1.12)	1.01 (0.92-1.11)
	Most vs. least	3804	11.1	1.26 (1.13-1.41)	1.01 (0.90-1.14)	1.00 (0.88-1.12)

		Items					
		Contacts (little vs. more)	9601	10.3	1.10 (1.01-1.19)	0.98 (0.90-1.07)	0.97 (0.89-1.05)
		Live alone (yes vs. no)	4602	11.5	1.22 (1.11-1.34)	1.05 (0.96-1.16)	1.05 (0.95-1.16)
Incident myocardial infarction		Social isolation					
		Moderately vs. least	8147	6.5	1.09 (0.97-1.22)	1.00 (0.89-1.12)	0.98 (0.88-1.11)
		Most vs. least	3804	7.3	1.26 (1.10-1.45)	1.02 (0.88-1.18)	1.01 (0.87-1.16)
		Items					
		Contacts (little vs. more)	9601	6.7	1.10 (0.99-1.21)	0.98 (0.88-1.09)	0.97 (0.87-1.07)
		Live alone (yes vs. no)	4602	7.3	1.18 (1.05-1.33)	1.03 (0.91-1.17)	1.03 (0.91-1.16)
Incident stroke		Social isolation					
		Moderately vs. least	8147	4.1	1.17 (1.01-1.35)	1.06 (0.92-1.23)	1.05 (0.91-1.22)
		Most vs. least	3804	4.3	1.25 (1.05-1.50)	1.00 (0.83-1.20)	0.98 (0.81-1.18)
		Items					
		Contacts (little vs. more)	9601	4.0	1.08 (0.95-1.23)	0.98 (0.85-1.11)	0.96 (0.84-1.10)
		Live alone (yes vs. no)	4602	4.8	1.29 (1.12-1.49)	1.10 (0.94-1.28)	1.10 (0.94-1.28)
<hr/>							
Fatal events							
Composites of fatal myocardial infarction or stroke		Social isolation					
		Moderately vs. least	8147	0.7	1.52 (1.05-2.20)	1.35 (0.92-1.96)	1.33 (0.92-1.95)
		Most vs. least	3804	1.2	2.55 (1.72-3.79)	1.90 (1.25-2.89)	1.89 (1.24-2.87)
		Items					

	Contacts (little vs. more)	9601	0.9	1.60 (1.18-2.18)	1.36 (1.00-1.87)	1.35 (0.98-1.85)
	Live alone (yes vs. no)	4602	1.1	1.97 (1.44-2.70)	1.60 (1.14-2.24)	1.60 (1.14-2.24)
Fatal myocardial infarction	Social isolation					
	Moderately vs. least	8147	0.5	1.41 (0.93-2.14)	1.26 (0.82-1.92)	1.26 (0.82-1.92)
	Most vs. least	3804	1.0	2.63 (1.69-4.08)	1.96 (1.23-3.13)	1.94 (1.22-3.10)
	Items					
	Contacts (little vs. more)	9601	0.7	1.57 (1.11-2.22)	1.34 (0.94-1.92)	1.33 (0.93-1.89)
	Live alone (yes vs. no)	4602	0.9	2.05 (1.44-2.91)	1.64 (1.13-2.40)	1.65 (1.13-2.40)
Fatal stroke	Social isolation					
	Moderately vs. least	8147	0.2	2.08 (0.94-4.60)	1.77 (0.79-3.96)	1.76 (0.78-3.93)
	Most vs. least	3804	0.2	2.24 (0.89-5.65)	1.60 (0.61-4.22)	1.62 (0.61-4.29)
	Items					
	Contacts (little vs. more)	9601	0.2	1.62 (0.84-3.13)	1.32 (0.67-2.59)	1.31 (0.66-2.57)
	Live alone (yes vs. no)	4602	0.2	1.86 (0.95-3.66)	1.57 (0.76-3.22)	1.60 (0.78-3.30)
<hr/>						
Non-fatal events						
Composites of non-fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8147	9.4	1.10 (1.00-1.21)	1.00 (0.91-1.11)	0.99 (0.90-1.10)
	Most vs. least	3804	9.9	1.19 (1.05-1.34)	0.96 (0.84-1.08)	0.94 (0.83-1.07)
	Items					
	Contacts (little vs. more)	9601	9.4	1.07 (0.98-1.16)	0.96 (0.88-1.05)	0.95 (0.87-1.03)
	Live alone (yes vs. no)	4602	10.4	1.17 (1.06-1.29)	1.01 (0.91-1.12)	1.01 (0.91-1.12)

Non-fatal myocardial infarction	Social isolation						
	Moderately vs. least	8147	5.9	1.07 (0.95-1.20)	0.98 (0.87-1.10)	0.97 (0.86-1.09)	
	Most vs. least	3804	6.3	1.17 (1.01-1.35)	0.95 (0.81-1.11)	0.94 (0.80-1.09)	
	Items						
	Contacts (little vs. more)	9601	6.0	1.06 (0.95-1.18)	0.95 (0.85-1.06)	0.94 (0.84-1.05)	
	Live alone (yes vs. no)	4602	6.3	1.11 (0.98-1.26)	0.98 (0.86-1.11)	0.97 (0.86-1.11)	
Non-fatal stroke	Social isolation						
	Moderately vs. least	8147	3.9	1.14 (0.98-1.32)	1.04 (0.90-1.21)	1.03 (0.89-1.20)	
	Most vs. least	3804	4.1	1.23 (1.02-1.47)	0.98 (0.81-1.18)	0.96 (0.79-1.16)	
	Items						
	Contacts (little vs. more)	9601	3.8	1.07 (0.93-1.22)	0.96 (0.84-1.10)	0.95 (0.83-1.09)	
	Live alone (yes vs. no)	4602	4.5	1.27 (1.10-1.47)	1.08 (0.92-1.26)	1.08 (0.93-1.26)	

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 5. Associations of loneliness with subsequent risk for mortality, myocardial infarction, and stroke in patients with type 2 diabetes mellitus

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Loneliness (yes vs. no)	1487	14.1	1.34 (1.18-1.53)	1.00 (0.87-1.14)	1.00 (0.87-1.14)
	Items					
	Lonely (yes vs. no)	4570	13.4	1.40 (1.29-1.53)	1.12 (1.02-1.22)	1.11 (1.01-1.21)
	Able to confide (never vs. usually)	3849	14.7	1.27 (1.16-1.38)	1.09 (1.00-1.19)	1.07 (0.98-1.17)
CVD mortality	Loneliness (yes vs. no)	1487	7.2	1.41 (1.17-1.69)	1.03 (0.85-1.24)	1.03 (0.85-1.24)
	Items					
	Lonely (yes vs. no)	4570	6.5	1.41 (1.24-1.59)	1.09 (0.96-1.25)	1.08 (0.95-1.24)
	Able to confide (never vs. usually)	3849	7.6	1.35 (1.20-1.53)	1.15 (1.01-1.30)	1.13 (0.99-1.28)
Overall						
Composites of incident myocardial infarction or stroke	Loneliness (yes vs. no)	1487	14.5	1.64 (1.43-1.87)	1.39 (1.21-1.59)	1.37 (1.19-1.57)
	Items					
	Lonely (yes vs. no)	4570	11.6	1.43 (1.31-1.57)	1.23 (1.12-1.36)	1.21 (1.10-1.34)
	Able to confide (never vs. usually)	3849	12.6	1.29 (1.17-1.42)	1.18 (1.07-1.31)	1.17 (1.06-1.29)
Incident myocardial infarction	Loneliness (yes vs. no)	1487	9.3	1.60 (1.36-1.89)	1.34 (1.13-1.59)	1.33 (1.12-1.57)
	Items					
	Lonely (yes vs. no)	4570	7.4	1.41 (1.25-1.58)	1.20 (1.06-1.35)	1.18 (1.04-1.33)

	Able to confide (never vs. usually)	3849	8.3	1.30 (1.16-1.46)	1.19 (1.06-1.35)	1.18 (1.05-1.33)
Incident stroke	Loneliness (yes vs. no)	1487	5.6	1.59 (1.28-1.96)	1.35 (1.09-1.68)	1.34 (1.07-1.66)
	Items					
	Lonely (yes vs. no)	4570	4.7	1.44 (1.24-1.67)	1.26 (1.07-1.47)	1.23 (1.05-1.44)
	Able to confide (never vs. usually)	3849	4.8	1.26 (1.09-1.47)	1.16 (0.99-1.35)	1.14 (0.98-1.34)
<hr/>						
Fatal events						
Composites of fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1487	1.1	1.77 (1.11-2.83)	1.27 (0.78-2.06)	1.27 (0.78-2.07)
	Items					
	Lonely (yes vs. no)	4570	0.9	1.67 (1.20-2.34)	1.32 (0.92-1.89)	1.29 (0.90-1.84)
	Able to confide (never vs. usually)	3849	1.1	1.62 (1.16-2.25)	1.33 (0.95-1.87)	1.31 (0.93-1.84)
Fatal myocardial infarction	Loneliness (yes vs. no)	1487	1.0	1.93 (1.16-3.22)	1.36 (0.80-2.32)	1.38 (0.81-2.34)
	Items					
	Lonely (yes vs. no)	4570	0.7	1.78 (1.22-2.58)	1.38 (0.93-2.07)	1.35 (0.90-2.02)
	Able to confide (never vs. usually)	3849	0.9	1.84 (1.28-2.64)	1.50 (1.03-2.18)	1.48 (1.02-2.16)
Fatal stroke	Loneliness (yes vs. no)	1487	0.2	1.18 (0.36-3.87)	0.91 (0.27-3.06)	0.88 (0.26-2.95)
	Items					
	Lonely (yes vs. no)	4570	0.2	1.29 (0.60-2.75)	1.07 (0.48-2.39)	1.03 (0.46-2.32)
	Able to confide (never vs. usually)	3849	0.2	0.91 (0.40-2.07)	0.77 (0.33-1.79)	0.74 (0.32-1.72)
<hr/>						
Non-fatal events						
Composites of non-fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1487	13.3	1.62 (1.41-1.86)	1.39 (1.20-1.60)	1.37 (1.19-1.58)

	Items					
	Lonely (yes vs. no)	4570	10.7	1.41 (1.28-1.55)	1.22 (1.10-1.36)	1.20 (1.08-1.34)
	Able to confide (never vs. usually)	3849	11.5	1.27 (1.14-1.40)	1.17 (1.06-1.30)	1.16 (1.05-1.29)
Non-fatal myocardial infarction	Loneliness (yes vs. no)	1487	8.3	1.57 (1.32-1.87)	1.33 (1.11-1.59)	1.32 (1.10-1.57)
	Items					
	Lonely (yes vs. no)	4570	6.7	1.37 (1.21-1.55)	1.18 (1.03-1.34)	1.16 (1.02-1.32)
	Able to confide (never vs. usually)	3849	7.4	1.25 (1.11-1.42)	1.16 (1.02-1.32)	1.15 (1.01-1.31)
Non-fatal stroke	Loneliness (yes vs. no)	1487	5.4	1.60 (1.29-1.99)	1.38 (1.11-1.72)	1.36 (1.09-1.70)
	Items					
	Lonely (yes vs. no)	4570	4.5	1.45 (1.25-1.68)	1.27 (1.08-1.48)	1.24 (1.06-1.46)
	Able to confide (never vs. usually)	3849	4.7	1.28 (1.10-1.50)	1.18 (1.01-1.38)	1.17 (0.99-1.37)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 6. Sensitivity analyses of joint associations of social isolation and loneliness with subsequent risk of mortality, myocardial infarction, and stroke in patients with type 2 diabetes mellitus

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1*	Model 2†	Model 3‡
				HR (95% CI)	HR (95% CI)	HR (95% CI)
Mortality						
All-cause mortality	No loneliness					
	Least social isolation	7108	10.3	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Moderately social isolation	7522	12.1	1.27 (1.16-1.38)	1.18 (1.08-1.29)	1.16 (1.06-1.27)
	Most social isolation	3243	15.0	1.67 (1.50-1.85)	1.36 (1.22-1.52)	1.33 (1.19-1.48)
	Loneliness					
	Least social isolation	301	9.8	1.15 (0.83-1.61)	1.02 (0.73-1.43)	1.02 (0.73-1.42)
	Moderately social isolation	625	13.1	1.56 (1.27-1.92)	1.17 (0.95-1.45)	1.16 (0.94-1.43)
	Most social isolation	561	17.7	1.99 (1.64-2.41)	1.35 (1.11-1.65)	1.32 (1.08-1.61)
	CVD mortality	No loneliness				
Least social isolation		7108	4.8	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Moderately social isolation		7522	6.0	1.37 (1.21-1.56)	1.25 (1.10-1.42)	1.22 (1.07-1.39)
Most social isolation		3243	7.4	1.79 (1.54-2.09)	1.40 (1.20-1.64)	1.36 (1.16-1.59)
Loneliness						
Least social isolation		301	4.4	1.12 (0.68-1.84)	0.98 (0.60-1.62)	0.97 (0.59-1.60)
Moderately social isolation		625	6.8	1.75 (1.31-2.34)	1.28 (0.95-1.72)	1.25 (0.93-1.69)
Most social isolation		561	9.3	2.26 (1.72-2.95)	1.47 (1.12-1.94)	1.44 (1.09-1.90)

Overall

Composites of incident myocardial infarction or stroke	No loneliness						
	Least social isolation	7108	9.5		1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Moderately social isolation	7522	9.8		1.10 (1.00-1.21)	1.03 (0.93-1.13)	1.02 (0.92-1.12)
	Most social isolation	3243	10.3		1.20 (1.06-1.36)	1.02 (0.90-1.16)	1.01 (0.89-1.14)
	Loneliness						
	Least social isolation	301	13.6		1.70 (1.27-2.28)	1.52 (1.13-2.04)	1.51 (1.12-2.02)
	Moderately social isolation	625	13.9		1.72 (1.40-2.12)	1.40 (1.13-1.73)	1.36 (1.10-1.68)
	Most social isolation	561	15.7		1.84 (1.49-2.28)	1.38 (1.11-1.71)	1.35 (1.08-1.68)
	Incident myocardial infarction	No loneliness					
Least social isolation		7108	6.2		1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Moderately social isolation		7522	6.3		1.09 (0.97-1.23)	1.02 (0.90-1.15)	1.01 (0.89-1.13)
Most social isolation		3243	6.8		1.21 (1.04-1.41)	1.04 (0.89-1.21)	1.02 (0.88-1.19)
Loneliness							
Least social isolation		301	9.7		1.85 (1.30-2.61)	1.64 (1.16-2.33)	1.63 (1.15-2.31)
Moderately social isolation		625	8.2		1.55 (1.19-2.03)	1.25 (0.95-1.64)	1.22 (0.93-1.60)
Most social isolation		561	10.4		1.84 (1.42-2.39)	1.35 (1.04-1.76)	1.32 (1.01-1.72)
Incident stroke		No loneliness					
	Least social isolation	7108	3.7		1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Moderately social isolation	7522	4.0		1.14 (0.98-1.33)	1.06 (0.91-1.24)	1.05 (0.90-1.23)
	Most social isolation	3243	4.0		1.21 (1.00-1.47)	1.01 (0.83-1.24)	0.99 (0.81-1.21)
	Loneliness						
	Least social isolation	301	5.0		1.57 (0.98-2.53)	1.41 (0.87-2.27)	1.37 (0.85-2.21)

	Moderately social isolation	625	5.8	1.85 (1.34-2.54)	1.50 (1.08-2.07)	1.46 (1.05-2.02)
	Most social isolation	561	5.6	1.70 (1.21-2.41)	1.28 (0.90-1.83)	1.26 (0.88-1.80)
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Fatal events						
Composites of fatal myocardial infarction or stroke	No loneliness					
	Least social isolation	7108	0.5	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Moderately social isolation	7522	0.7	1.54 (1.05-2.27)	1.40 (0.95-2.06)	1.38 (0.93-2.04)
	Most social isolation	3243	1.1	2.45 (1.60-3.75)	1.92 (1.23-2.99)	1.89 (1.21-2.96)
	Loneliness					
	Least social isolation	301	0.8	1.96 (0.61-6.32)	1.76 (0.54-5.71)	1.66 (0.51-5.38)
	Moderately social isolation	625	0.8	1.90 (0.81-4.48)	1.45 (0.61-3.45)	1.45 (0.61-3.45)
	Most social isolation	561	1.7	3.72 (1.91-7.22)	2.55 (1.28-5.07)	2.54 (1.28-5.08)
	Fatal myocardial infarction	No loneliness				
Least social isolation		7108	0.4	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Moderately social isolation		7522	0.5	1.47 (0.95-2.28)	1.34 (0.86-2.09)	1.34 (0.86-2.08)
Most social isolation		3243	0.9	2.51 (1.56-4.04)	1.99 (1.21-3.27)	1.96 (1.19-3.23)
Loneliness						
Least social isolation		301	0.8	2.48 (0.76-8.08)	2.25 (0.69-7.38)	2.15 (0.65-7.04)
Moderately social isolation		625	0.5	1.61 (0.57-4.53)	1.24 (0.43-3.53)	1.25 (0.44-3.58)
Most social isolation		561	1.5	4.27 (2.10-8.66)	2.90 (1.39-6.06)	2.92 (1.39-6.10)
Fatal stroke		No loneliness				
	Least social isolation	7108	0.1	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]

	Moderately social isolation	7522	0.2	1.93 (0.86-4.34)	1.65 (0.73-3.73)	1.63 (0.72-3.69)
	Most social isolation	3243	0.2	2.25 (0.87-5.85)	1.59 (0.59-4.29)	1.60 (0.59-4.34)
	Loneliness					
	Least social isolation	301	0.0	0.00 (0.00-Inf)	0.00 (0.00-Inf)	0.00 (0.00-Inf)
	Moderately social isolation	625	0.3	3.06 (0.66-14.24)	2.27 (0.47-10.89)	2.13 (0.44-10.28)
	Most social isolation	561	0.2	1.64 (0.21-12.95)	1.14 (0.14-9.29)	1.14 (0.14-9.37)

Non-fatal events						
Composites of non-fatal myocardial infarction or stroke	No loneliness					
	Least social isolation	7108	9.0	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Moderately social isolation	7522	9.1	1.08 (0.98-1.19)	1.01 (0.91-1.12)	1.00 (0.90-1.11)
	Most social isolation	3243	9.2	1.13 (1.00-1.29)	0.97 (0.85-1.10)	0.95 (0.83-1.09)
	Loneliness					
	Least social isolation	301	12.7	1.68 (1.24-2.27)	1.50 (1.11-2.04)	1.49 (1.10-2.02)
	Moderately social isolation	625	13.0	1.70 (1.37-2.12)	1.39 (1.12-1.73)	1.35 (1.08-1.68)
	Most social isolation	561	13.9	1.72 (1.38-2.16)	1.30 (1.03-1.63)	1.27 (1.01-1.60)
	Non-fatal myocardial infarction	No loneliness				
Least social isolation		7108	5.8	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Moderately social isolation		7522	5.8	1.06 (0.94-1.20)	0.99 (0.88-1.13)	0.98 (0.87-1.12)
Most social isolation		3243	5.9	1.12 (0.96-1.32)	0.97 (0.82-1.14)	0.96 (0.81-1.13)
Loneliness						
Least social isolation		301	8.8	1.80 (1.25-2.58)	1.60 (1.11-2.30)	1.59 (1.11-2.30)
Moderately social isolation		625	7.7	1.54 (1.17-2.04)	1.25 (0.94-1.66)	1.22 (0.92-1.62)

Non-fatal stroke	Most social isolation	561	8.8	1.66 (1.26-2.20)	1.23 (0.93-1.64)	1.20 (0.90-1.60)
	No loneliness					
	Least social isolation	7108	3.6	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Moderately social isolation	7522	3.8	1.12 (0.96-1.31)	1.04 (0.89-1.22)	1.03 (0.88-1.21)
	Most social isolation	3243	3.8	1.18 (0.97-1.44)	0.99 (0.81-1.21)	0.97 (0.79-1.19)
	Loneliness					
	Least social isolation	301	5.0	1.62 (1.01-2.60)	1.45 (0.90-2.34)	1.42 (0.88-2.29)
	Moderately social isolation	625	5.5	1.81 (1.31-2.51)	1.47 (1.06-2.06)	1.44 (1.03-2.00)
	Most social isolation	561	5.5	1.71 (1.20-2.42)	1.29 (0.90-1.85)	1.27 (0.88-1.81)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, and hyperlipidaemia;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 7. Sensitivity analyses of associations of social isolation and its items with subsequent risk for mortality, myocardial infarction, and stroke in sample with complete cases

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Social isolation					
	Moderately vs. least	4674	12.6	1.35 (1.20-1.50)	1.27 (1.13-1.42)	1.25 (1.12-1.40)
	Most vs. least	2145	14.3	1.59 (1.39-1.81)	1.34 (1.17-1.54)	1.33 (1.16-1.53)
	Items					
	Contacts (little vs. more)	5424	12.7	1.24 (1.12-1.36)	1.14 (1.03-1.26)	1.13 (1.02-1.25)
	Live alone (yes vs. no)	2657	15.7	1.52 (1.37-1.69)	1.32 (1.18-1.48)	1.33 (1.19-1.49)
CVD mortality	Social isolation					
	Moderately vs. least	4674	6.1	1.40 (1.19-1.65)	1.30 (1.10-1.53)	1.28 (1.09-1.51)
	Most vs. least	2145	6.8	1.62 (1.34-1.96)	1.31 (1.07-1.60)	1.30 (1.06-1.60)
	Items					
	Contacts (little vs. more)	5424	6.2	1.28 (1.11-1.48)	1.15 (1.00-1.33)	1.14 (0.98-1.32)
	Live alone (yes vs. no)	2657	7.4	1.52 (1.30-1.77)	1.31 (1.12-1.54)	1.33 (1.13-1.56)
Overall						
Composites of incident myocardial infarction or stroke	Social isolation					
	Moderately vs. least	4674	10.3	1.13 (1.00-1.28)	1.05 (0.93-1.18)	1.03 (0.92-1.17)
	Most vs. least	2145	11.0	1.23 (1.07-1.43)	1.01 (0.86-1.17)	0.99 (0.85-1.16)

	Items					
	Contacts (little vs. more)	5424	10.4	1.11 (0.99-1.23)	1.00 (0.90-1.12)	0.99 (0.89-1.11)
	Live alone (yes vs. no)	2657	11.3	1.18 (1.04-1.33)	1.02 (0.90-1.17)	1.02 (0.89-1.16)
Incident myocardial infarction	Social isolation					
	Moderately vs. least	4674	7.0	1.21 (1.04-1.40)	1.12 (0.97-1.30)	1.11 (0.96-1.29)
	Most vs. least	2145	7.4	1.30 (1.08-1.56)	1.08 (0.89-1.30)	1.07 (0.88-1.29)
	Items					
	Contacts (little vs. more)	5424	7.2	1.18 (1.04-1.35)	1.08 (0.95-1.24)	1.08 (0.94-1.23)
	Live alone (yes vs. no)	2657	7.2	1.13 (0.97-1.32)	0.99 (0.84-1.16)	0.98 (0.83-1.15)
Incident stroke	Social isolation					
	Moderately vs. least	4674	3.9	1.04 (0.86-1.25)	0.95 (0.79-1.16)	0.94 (0.78-1.14)
	Most vs. least	2145	4.2	1.13 (0.89-1.43)	0.91 (0.71-1.17)	0.90 (0.70-1.15)
	Items					
	Contacts (little vs. more)	5424	3.9	0.99 (0.84-1.18)	0.89 (0.75-1.06)	0.88 (0.74-1.04)
	Live alone (yes vs. no)	2657	4.6	1.23 (1.02-1.49)	1.09 (0.89-1.33)	1.08 (0.88-1.32)
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	Fatal events					
Composites of fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	4674	0.7	1.42 (0.87-2.32)	1.38 (0.84-2.27)	1.36 (0.83-2.24)
	Most vs. least	2145	0.9	1.92 (1.09-3.36)	1.71 (0.95-3.08)	1.71 (0.95-3.08)
	Items					
	Contacts (little vs. more)	5424	0.7	1.26 (0.83-1.93)	1.19 (0.77-1.83)	1.19 (0.77-1.84)

	Live alone (yes vs. no)	2657	0.9	1.72 (1.10-2.70)	1.58 (0.98-2.55)	1.54 (0.95-2.50)
Fatal myocardial infarction	Social isolation					
	Moderately vs. least	4674	0.5	1.48 (0.84-2.60)	1.44 (0.82-2.55)	1.43 (0.81-2.53)
	Most vs. least	2145	0.7	2.20 (1.18-4.10)	1.98 (1.03-3.80)	1.99 (1.03-3.82)
	Items					
	Contacts (little vs. more)	5424	0.6	1.28 (0.80-2.06)	1.20 (0.74-1.95)	1.21 (0.74-1.97)
Fatal stroke	Live alone (yes vs. no)	2657	0.8	1.93 (1.18-3.18)	1.80 (1.06-3.05)	1.77 (1.04-3.01)
	Social isolation					
	Moderately vs. least	4674	0.1	1.23 (0.45-3.41)	1.20 (0.43-3.36)	1.19 (0.42-3.39)
	Most vs. least	2145	0.1	1.06 (0.27-4.10)	0.89 (0.22-3.66)	0.93 (0.22-3.98)
	Items					
	Contacts (little vs. more)	5424	0.1	1.19 (0.47-3.01)	1.12 (0.43-2.90)	1.22 (0.46-3.23)
	Live alone (yes vs. no)	2657	0.1	1.04 (0.34-3.18)	0.89 (0.28-2.85)	0.82 (0.25-2.72)
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Non-fatal events						
Composites of non-fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	4674	9.7	1.12 (0.99-1.26)	1.03 (0.91-1.16)	1.02 (0.90-1.15)
	Most vs. least	2145	10.1	1.19 (1.02-1.39)	0.97 (0.82-1.14)	0.96 (0.81-1.12)
	Items					
	Contacts (little vs. more)	5424	9.8	1.10 (0.98-1.23)	1.00 (0.89-1.12)	0.99 (0.89-1.11)
	Live alone (yes vs. no)	2657	10.4	1.14 (1.00-1.30)	0.99 (0.87-1.13)	0.98 (0.86-1.13)
Non-fatal myocardial infarction	Social isolation					

	Moderately vs. least	4674	6.5	1.19 (1.02-1.39)	1.10 (0.94-1.29)	1.09 (0.94-1.28)
	Most vs. least	2145	6.6	1.24 (1.02-1.50)	1.02 (0.84-1.24)	1.01 (0.83-1.23)
	Items					
	Contacts (little vs. more)	5424	6.6	1.18 (1.03-1.35)	1.07 (0.93-1.23)	1.07 (0.93-1.23)
	Live alone (yes vs. no)	2657	6.4	1.08 (0.92-1.27)	0.94 (0.79-1.11)	0.93 (0.78-1.10)
Non-fatal stroke	Social isolation					
	Moderately vs. least	4674	3.8	1.03 (0.85-1.25)	0.95 (0.78-1.15)	0.94 (0.77-1.14)
	Most vs. least	2145	4.1	1.13 (0.89-1.43)	0.91 (0.71-1.17)	0.89 (0.70-1.15)
	Items					
	Contacts (little vs. more)	5424	3.7	0.99 (0.83-1.17)	0.88 (0.74-1.05)	0.87 (0.73-1.04)
	Live alone (yes vs. no)	2657	4.5	1.24 (1.02-1.51)	1.09 (0.89-1.34)	1.09 (0.89-1.34)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 8. Sensitivity analyses of associations of loneliness and its items with subsequent risk for mortality, myocardial infarction, and stroke in sample with complete cases

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Loneliness (yes vs. no)	848	12.7	1.19 (0.99-1.42)	0.91 (0.76-1.10)	0.91 (0.76-1.10)
	Items					
	Lonely (yes vs. no)	2516	11.9	1.21 (1.08-1.36)	0.99 (0.87-1.12)	0.98 (0.86-1.11)
	Able to confide (never vs. usually)	2180	13.7	1.16 (1.03-1.30)	1.01 (0.89-1.14)	1.00 (0.89-1.13)
CVD mortality	Loneliness (yes vs. no)	848	6.0	1.17 (0.90-1.52)	0.90 (0.69-1.18)	0.92 (0.70-1.20)
	Items					
	Lonely (yes vs. no)	2516	5.5	1.19 (1.00-1.41)	0.98 (0.81-1.17)	0.97 (0.80-1.16)
	Able to confide (never vs. usually)	2180	7.1	1.27 (1.07-1.50)	1.11 (0.93-1.31)	1.09 (0.92-1.30)
Overall						
Composites of incident myocardial infarction or stroke	Loneliness (yes vs. no)	848	14.5	1.60 (1.34-1.91)	1.36 (1.13-1.63)	1.34 (1.12-1.61)
	Items					
	Lonely (yes vs. no)	2516	11.7	1.41 (1.25-1.60)	1.24 (1.09-1.42)	1.22 (1.07-1.39)
	Able to confide (never vs. usually)	2180	12.9	1.31 (1.16-1.49)	1.20 (1.06-1.37)	1.19 (1.05-1.35)
Incident myocardial infarction	Loneliness (yes vs. no)	848	8.8	1.44 (1.15-1.80)	1.20 (0.96-1.51)	1.19 (0.94-1.50)
	Items					
	Lonely (yes vs. no)	2516	7.6	1.38 (1.18-1.61)	1.18 (1.00-1.39)	1.16 (0.98-1.36)

	Able to confide (never vs. usually)	2180	8.4	1.27 (1.08-1.48)	1.16 (0.99-1.36)	1.14 (0.98-1.34)
Incident stroke	Loneliness (yes vs. no)	848	6.0	1.69 (1.29-2.21)	1.45 (1.10-1.91)	1.42 (1.08-1.88)
	Items					
	Lonely (yes vs. no)	2516	4.7	1.42 (1.16-1.72)	1.29 (1.04-1.58)	1.25 (1.02-1.54)
	Able to confide (never vs. usually)	2180	5.1	1.34 (1.10-1.63)	1.23 (1.00-1.50)	1.21 (0.99-1.49)
<hr/>						
Fatal events						
Composites of fatal myocardial infarction or stroke	Loneliness (yes vs. no)	848	0.7	1.20 (0.55-2.61)	0.95 (0.43-2.09)	0.93 (0.42-2.05)
	Items					
	Lonely (yes vs. no)	2516	0.6	1.26 (0.75-2.10)	1.06 (0.61-1.84)	1.02 (0.59-1.77)
	Able to confide (never vs. usually)	2180	0.9	1.42 (0.88-2.29)	1.28 (0.78-2.08)	1.26 (0.77-2.06)
Fatal myocardial infarction	Loneliness (yes vs. no)	848	0.6	1.31 (0.56-3.03)	0.99 (0.42-2.34)	0.99 (0.42-2.35)
	Items					
	Lonely (yes vs. no)	2516	0.5	1.36 (0.77-2.39)	1.11 (0.61-2.04)	1.08 (0.59-1.99)
	Able to confide (never vs. usually)	2180	0.8	1.62 (0.96-2.72)	1.42 (0.83-2.42)	1.43 (0.84-2.45)
Fatal stroke	Loneliness (yes vs. no)	848	0.1	0.81 (0.11-6.13)	0.74 (0.09-5.79)	0.62 (0.08-5.00)
	Items					
	Lonely (yes vs. no)	2516	0.1	0.90 (0.26-3.14)	0.83 (0.22-3.17)	0.73 (0.19-2.82)
	Able to confide (never vs. usually)	2180	0.1	0.79 (0.23-2.74)	0.77 (0.22-2.76)	0.72 (0.20-2.63)
<hr/>						
Non-fatal events						

Composites of non-fatal myocardial infarction or stroke	Loneliness (yes vs. no)	848	13.8	1.62 (1.35-1.94)	1.38 (1.15-1.67)	1.36 (1.13-1.65)
	Items					
	Lonely (yes vs. no)	2516	11.1	1.42 (1.25-1.61)	1.25 (1.09-1.44)	1.23 (1.07-1.41)
	Able to confide (never vs. usually)	2180	12.0	1.30 (1.14-1.48)	1.19 (1.04-1.36)	1.18 (1.03-1.35)
Non-fatal myocardial infarction	Loneliness (yes vs. no)	848	8.2	1.45 (1.15-1.83)	1.22 (0.96-1.55)	1.20 (0.95-1.52)
	Items					
	Lonely (yes vs. no)	2516	7.0	1.38 (1.18-1.62)	1.19 (1.00-1.40)	1.16 (0.98-1.38)
	Able to confide (never vs. usually)	2180	7.6	1.24 (1.05-1.45)	1.13 (0.96-1.34)	1.12 (0.95-1.32)
Non-fatal stroke	Loneliness (yes vs. no)	848	5.9	1.72 (1.31-2.26)	1.48 (1.12-1.96)	1.46 (1.10-1.93)
	Items					
	Lonely (yes vs. no)	2516	4.6	1.43 (1.18-1.75)	1.30 (1.06-1.61)	1.27 (1.03-1.57)
	Able to confide (never vs. usually)	2180	5.0	1.36 (1.11-1.66)	1.25 (1.02-1.53)	1.23 (1.01-1.52)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 9. Sensitivity analyses of associations of social isolation and its items with subsequent risk for mortality, myocardial infarction, and stroke in sample with imputed data on exposures

Outcomes	Exposures	N*	Incident rate (per 1000 person-years)	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)	Model 3§ HR (95% CI)
Mortality						
All-cause mortality	Social isolation					
	Moderately vs. least	8984	12.1	1.29 (1.18-1.40)	1.17 (1.08-1.28)	1.16 (1.07-1.27)
	Most vs. least	4242	15.2	1.71 (1.56-1.89)	1.36 (1.23-1.50)	1.33 (1.20-1.47)
	Items					
	Contacts (little vs. more)	10,681	12.8	1.26 (1.18-1.36)	1.14 (1.06-1.22)	1.11 (1.03-1.20)
	Live alone (yes vs. no)	5026	16.2	1.55 (1.43-1.67)	1.28 (1.18-1.39)	1.28 (1.18-1.39)
CVD mortality	Social isolation					
	Moderately vs. least	8984	6.1	1.41 (1.25-1.59)	1.26 (1.11-1.42)	1.24 (1.09-1.40)
	Most vs. least	4242	7.7	1.90 (1.66-2.18)	1.44 (1.24-1.66)	1.40 (1.21-1.62)
	Items					
	Contacts (little vs. more)	10,681	6.5	1.37 (1.24-1.52)	1.19 (1.07-1.33)	1.16 (1.05-1.29)
	Live alone (yes vs. no)	5026	8.2	1.64 (1.47-1.83)	1.34 (1.19-1.51)	1.35 (1.21-1.52)
Overall						
Composites of incident myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8984	10.1	1.11 (1.02-1.22)	1.02 (0.93-1.12)	1.01 (0.92-1.11)
	Most vs. least	4242	11.0	1.26 (1.13-1.40)	1.01 (0.90-1.13)	1.00 (0.89-1.12)

	Items					
	Contacts (little vs. more)	10,681	10.3	1.10 (1.02-1.19)	0.99 (0.92-1.08)	0.98 (0.91-1.07)
	Live alone (yes vs. no)	5026	11.4	1.21 (1.10-1.32)	1.04 (0.94-1.14)	1.04 (0.94-1.14)
Incident myocardial infarction	Social isolation					
	Moderately vs. least	8984	6.5	1.08 (0.97-1.21)	0.99 (0.89-1.11)	0.98 (0.88-1.10)
	Most vs. least	4242	7.2	1.24 (1.09-1.42)	1.01 (0.88-1.16)	1.00 (0.87-1.15)
	Items					
	Contacts (little vs. more)	10,681	6.7	1.09 (0.99-1.20)	0.98 (0.89-1.08)	0.97 (0.88-1.07)
	Live alone (yes vs. no)	5026	7.3	1.18 (1.05-1.32)	1.03 (0.92-1.16)	1.03 (0.91-1.16)
Incident stroke	Social isolation					
	Moderately vs. least	8984	4.1	1.17 (1.02-1.35)	1.07 (0.93-1.24)	1.06 (0.92-1.23)
	Most vs. least	4242	4.3	1.29 (1.09-1.53)	1.02 (0.86-1.23)	1.01 (0.84-1.21)
	Items					
	Contacts (little vs. more)	10,681	4.1	1.12 (0.99-1.27)	1.01 (0.89-1.15)	1.00 (0.88-1.14)
	Live alone (yes vs. no)	5026	4.7	1.25 (1.09-1.44)	1.05 (0.91-1.22)	1.05 (0.91-1.22)
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Fatal events						
Composites of fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8984	0.7	1.47 (1.02-2.11)	1.29 (0.89-1.86)	1.28 (0.89-1.85)
	Most vs. least	4242	1.2	2.54 (1.74-3.71)	1.88 (1.25-2.81)	1.86 (1.24-2.79)
	Items					

	Contacts (little vs. more)	10,681	0.9	1.61 (1.19-2.17)	1.37 (1.01-1.86)	1.36 (1.00-1.85)
	Live alone (yes vs. no)	5026	1.1	1.98 (1.47-2.67)	1.59 (1.15-2.19)	1.58 (1.15-2.19)
Fatal myocardial infarction	Social isolation					
	Moderately vs. least	8984	0.5	1.32 (0.87-1.99)	1.16 (0.76-1.76)	1.16 (0.76-1.76)
	Most vs. least	4242	0.9	2.45 (1.61-3.74)	1.81 (1.16-2.84)	1.79 (1.14-2.82)
	Items					
	Contacts (little vs. more)	10,681	0.7	1.50 (1.07-2.10)	1.27 (0.90-1.80)	1.26 (0.89-1.79)
	Live alone (yes vs. no)	5026	0.9	2.04 (1.45-2.85)	1.65 (1.15-2.37)	1.65 (1.14-2.37)
Fatal stroke	Social isolation					
	Moderately vs. least	8984	0.2	2.28 (1.04-4.99)	1.95 (0.88-4.30)	1.92 (0.87-4.24)
	Most vs. least	4242	0.2	2.95 (1.24-7.02)	2.10 (0.85-5.23)	2.12 (0.85-5.28)
	Items					
	Contacts (little vs. more)	10,681	0.2	1.96 (1.04-3.69)	1.66 (0.87-3.17)	1.63 (0.85-3.13)
	Live alone (yes vs. no)	5026	0.3	1.94 (1.03-3.65)	1.48 (0.75-2.91)	1.51 (0.76-2.97)
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Non-fatal events						
Composites of non-fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8984	9.4	1.10 (1.00-1.20)	1.01 (0.92-1.11)	1.00 (0.91-1.10)
	Most vs. least	4242	9.8	1.18 (1.06-1.33)	0.96 (0.85-1.08)	0.95 (0.84-1.07)
	Items					
	Contacts (little vs. more)	10,681	9.4	1.07 (0.99-1.17)	0.97 (0.89-1.06)	0.96 (0.88-1.05)
	Live alone (yes vs. no)	5026	10.2	1.15 (1.05-1.26)	1.00 (0.90-1.10)	0.99 (0.90-1.10)

Non-fatal myocardial infarction	Social isolation					
	Moderately vs. least	8984	6.0	1.06 (0.95-1.19)	0.98 (0.87-1.10)	0.97 (0.86-1.09)
	Most vs. least	4242	6.3	1.16 (1.00-1.33)	0.95 (0.82-1.10)	0.94 (0.81-1.09)
	Items					
	Contacts (little vs. more)	10,681	6.0	1.06 (0.95-1.17)	0.96 (0.86-1.06)	0.95 (0.85-1.05)
	Live alone (yes vs. no)	5026	6.3	1.11 (0.99-1.25)	0.98 (0.87-1.11)	0.98 (0.86-1.11)
Non-fatal stroke	Social isolation					
	Moderately vs. least	8984	3.9	1.15 (0.99-1.32)	1.05 (0.91-1.21)	1.04 (0.90-1.20)
	Most vs. least	4242	4.1	1.25 (1.05-1.49)	0.99 (0.83-1.19)	0.98 (0.81-1.18)
	Items					
	Contacts (little vs. more)	10,681	3.9	1.10 (0.97-1.25)	0.99 (0.87-1.13)	0.98 (0.86-1.12)
	Live alone (yes vs. no)	5026	4.4	1.23 (1.06-1.42)	1.03 (0.89-1.20)	1.04 (0.89-1.20)

*Included the participants with responses of either “prefer not to answer” or “do not know”, which were regarded as missing data and multiply imputed.

†Model 1 adjusted for age and sex;

‡Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

§Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 10. Sensitivity analyses of associations of loneliness and its items with subsequent risk for mortality, myocardial infarction, and stroke in sample with imputed data on exposures

Outcomes	Exposures	N*	Incident rate (per 1000 person-years)	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)	Model 3§ HR (95% CI)
Mortality						
All-cause mortality	Loneliness (yes vs. no)	1648	14.1	1.37 (1.20-1.55)	1.01 (0.89-1.15)	1.01 (0.89-1.15)
	Items					
	Lonely (yes vs. no)	5075	13.3	1.40 (1.29-1.53)	1.12 (1.02-1.22)	1.11 (1.02-1.21)
CVD mortality	Able to confide (never vs. usually)	4268	14.7	1.27 (1.17-1.39)	1.09 (0.99-1.19)	1.07 (0.98-1.17)
	Loneliness (yes vs. no)	1648	7.1	1.43 (1.20-1.72)	1.03 (0.86-1.25)	1.04 (0.86-1.25)
	Items					
	Lonely (yes vs. no)	5075	6.5	1.42 (1.26-1.60)	1.10 (0.97-1.25)	1.09 (0.96-1.24)
	Able to confide (never vs. usually)	4268	7.5	1.35 (1.20-1.52)	1.13 (1.00-1.27)	1.11 (0.99-1.26)
Overall						
Composites of incident myocardial infarction or stroke	Loneliness (yes vs. no)	1648	14.3	1.60 (1.41-1.83)	1.35 (1.18-1.55)	1.34 (1.17-1.53)
	Items					
	Lonely (yes vs. no)	5075	11.5	1.42 (1.30-1.56)	1.22 (1.11-1.35)	1.21 (1.09-1.33)
Incident myocardial infarction	Able to confide (never vs. usually)	4268	12.4	1.27 (1.16-1.40)	1.17 (1.06-1.28)	1.16 (1.05-1.27)
	Loneliness (yes vs. no)	1648	9.2	1.56 (1.32-1.83)	1.31 (1.10-1.55)	1.29 (1.09-1.53)
	Items					
	Lonely (yes vs. no)	5075	7.4	1.40 (1.25-1.56)	1.19 (1.06-1.34)	1.18 (1.04-1.32)
	Able to confide (never vs. usually)	4268	8.2	1.28 (1.14-1.43)	1.17 (1.04-1.32)	1.16 (1.03-1.31)
Incident stroke	Loneliness (yes vs. no)	1648	5.6	1.60 (1.31-1.97)	1.35 (1.09-1.67)	1.33 (1.08-1.65)
	Items					
	Lonely (yes vs. no)	5075	4.7	1.45 (1.26-1.67)	1.25 (1.08-1.46)	1.23 (1.06-1.43)

	Able to confide (never vs. usually)	4268	4.8	1.28 (1.11-1.48)	1.16 (1.00-1.35)	1.15 (0.99-1.33)
Fatal events						
Composites of fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1648	1.2	1.70 (1.07-2.69)	1.20 (0.74-1.94)	1.19 (0.74-1.93)
	Items					
	Lonely (yes vs. no)	5075	1.0	1.64 (1.19-2.27)	1.26 (0.89-1.79)	1.23 (0.87-1.75)
	Able to confide (never vs. usually)	4268	1.1	1.51 (1.09-2.10)	1.23 (0.88-1.72)	1.20 (0.86-1.69)
Fatal myocardial infarction	Loneliness (yes vs. no)	1648	0.9	1.79 (1.07-2.97)	1.30 (0.77-2.20)	1.30 (0.77-2.20)
	Items					
	Lonely (yes vs. no)	5075	0.7	1.67 (1.16-2.41)	1.32 (0.89-1.95)	1.29 (0.87-1.91)
	Able to confide (never vs. usually)	4268	0.9	1.71 (1.19-2.46)	1.41 (0.97-2.05)	1.38 (0.95-2.01)
Fatal Stroke	Loneliness (yes vs. no)	1648	0.3	1.34 (0.43-4.15)	0.88 (0.27-2.84)	0.86 (0.27-2.77)
	Items					
	Lonely (yes vs. no)	5075	0.2	1.50 (0.74-3.05)	1.07 (0.50-2.29)	1.04 (0.49-2.23)
	Able to confide (never vs. usually)	4268	0.2	0.88 (0.40-1.97)	0.69 (0.30-1.56)	0.65 (0.29-1.49)
Non-fatal events						
Composites of non-fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1648	13.1	1.59 (1.38-1.82)	1.36 (1.18-1.56)	1.34 (1.17-1.55)
	Items					
	Lonely (yes vs. no)	5075	10.5	1.40 (1.27-1.54)	1.22 (1.10-1.34)	1.20 (1.08-1.33)
	Able to confide (never vs. usually)	4268	11.3	1.26 (1.14-1.38)	1.16 (1.05-1.28)	1.15 (1.04-1.27)
Non-fatal myocardial infarction	Loneliness (yes vs. no)	1648	8.2	1.53 (1.29-1.82)	1.30 (1.09-1.56)	1.29 (1.08-1.54)
	Items					

	Lonely (yes vs. no)	5075	6.6	1.37 (1.22-1.54)	1.18 (1.04-1.34)	1.16 (1.03-1.32)
	Able to confide (never vs. usually)	4268	7.3	1.24 (1.09-1.40)	1.15 (1.01-1.30)	1.14 (1.00-1.29)
Non-fatal stroke	Loneliness (yes vs. no)	1648	5.4	1.61 (1.31-1.99)	1.38 (1.11-1.71)	1.36 (1.10-1.69)
	Items					
	Lonely (yes vs. no)	5075	4.5	1.45 (1.26-1.68)	1.26 (1.08-1.47)	1.24 (1.07-1.45)
	Able to confide (never vs. usually)	4268	4.7	1.30 (1.12-1.51)	1.19 (1.02-1.39)	1.18 (1.01-1.37)

*Included the participants with responses of either “prefer not to answer” or “do not know”, which were regarded as missing data and multiply imputed.

†Model 1 adjusted for age and sex;

‡Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

§Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 11. Sensitivity analyses of associations of social isolation and its items with subsequent risk for mortality, myocardial infarction, and stroke after excluding events occurring within the first two years

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Social isolation					
	Moderately vs. least	8083	11.5	1.28 (1.17-1.39)	1.18 (1.08-1.29)	1.16 (1.06-1.27)
	Most vs. least	3769	14.6	1.71 (1.55-1.89)	1.37 (1.23-1.53)	1.34 (1.20-1.49)
	Items					
	Contacts (little vs. more)	9529	12.3	1.26 (1.17-1.36)	1.14 (1.06-1.24)	1.12 (1.03-1.21)
CVD mortality	Social isolation					
	Moderately vs. least	8083	5.8	1.38 (1.22-1.57)	1.25 (1.10-1.42)	1.22 (1.07-1.39)
	Most vs. least	3769	7.4	1.87 (1.62-2.16)	1.44 (1.23-1.68)	1.39 (1.19-1.62)
	Items					
	Contacts (little vs. more)	9529	6.2	1.35 (1.21-1.51)	1.19 (1.06-1.33)	1.15 (1.03-1.29)
	Live alone (yes vs. no)	4548	7.8	1.63 (1.45-1.83)	1.36 (1.20-1.53)	1.37 (1.21-1.55)
Overall						
Composites of incident myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8013	9.3	1.12 (1.01-1.23)	1.02 (0.92-1.13)	1.01 (0.91-1.11)
	Most vs. least	3736	10.1	1.25 (1.11-1.41)	1.01 (0.89-1.14)	0.99 (0.88-1.12)
	Items					
	Contacts (little vs. more)	9445	9.3	1.09 (1.00-1.19)	0.98 (0.89-1.07)	0.96 (0.88-1.05)

Incident myocardial infarction	Live alone (yes vs. no)	4505	10·5	1·21 (1·10-1·34)	1·05 (0·94-1·16)	1·04 (0·94-1·16)
	Social isolation					
	Moderately vs. least	8046	6·0	1·09 (0·97-1·23)	1·00 (0·88-1·12)	0·99 (0·87-1·11)
	Most vs. least	3751	6·8	1·27 (1·10-1·46)	1·02 (0·88-1·18)	1·00 (0·86-1·17)
	Items					
	Contacts (little vs. more)	9483	6·2	1·09 (0·98-1·21)	0·98 (0·88-1·09)	0·96 (0·87-1·08)
Incident stroke	Live alone (yes vs. no)	4527	6·8	1·19 (1·05-1·34)	1·03 (0·91-1·17)	1·02 (0·90-1·16)
	Social isolation					
	Moderately vs. least	8049	3·7	1·17 (1·00-1·36)	1·07 (0·91-1·25)	1·06 (0·91-1·24)
	Most vs. least	3754	3·8	1·24 (1·03-1·50)	0·99 (0·82-1·21)	0·98 (0·80-1·20)
	Items					
	Contacts (little vs. more)	9491	3·6	1·08 (0·94-1·24)	0·97 (0·85-1·12)	0·96 (0·83-1·10)
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Fatal events						
Composites of fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8083	0·7	1·47 (1·01-2·16)	1·32 (0·89-1·94)	1·30 (0·88-1·92)
	Most vs. least	3769	1·0	2·27 (1·50-3·45)	1·71 (1·10-2·66)	1·70 (1·09-2·64)
	Items					
		Contacts (little vs. more)	9529	0·8	1·48 (1·08-2·04)	1·26 (0·91-1·75)
	Live alone (yes vs. no)	4548	1·0	1·89 (1·36-2·63)	1·58 (1·11-2·24)	1·57 (1·10-2·25)

Fatal myocardial infarction	Social isolation					
	Moderately vs. least	8083	0·5	1·31 (0·85-2·02)	1·17 (0·75-1·81)	1·16 (0·75-1·81)
	Most vs. least	3769	0·8	2·34 (1·48-3·70)	1·73 (1·07-2·82)	1·71 (1·05-2·79)
	Items					
	Contacts (little vs. more)	9529	0·6	1·42 (0·99-2·04)	1·21 (0·84-1·75)	1·19 (0·82-1·73)
	Live alone (yes vs. no)	4548	0·8	2·01 (1·39-2·91)	1·65 (1·11-2·46)	1·65 (1·11-2·45)
Fatal stroke	Social isolation					
	Moderately vs. least	8083	0·2	2·35 (1·03-5·37)	2·07 (0·89-4·77)	2·03 (0·88-4·70)
	Most vs. least	3769	0·2	1·98 (0·72-5·48)	1·51 (0·52-4·36)	1·53 (0·53-4·41)
	Items					
	Contacts (little vs. more)	9529	0·2	1·59 (0·80-3·17)	1·35 (0·67-2·72)	1·33 (0·66-2·69)
	Live alone (yes vs. no)	4548	0·2	1·64 (0·80-3·37)	1·44 (0·67-3·08)	1·46 (0·68-3·14)
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Non-fatal events						
Composites of non-fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8013	8·6	1·10 (0·99-1·21)	1·00 (0·91-1·11)	0·99 (0·90-1·10)
	Most vs. least	3736	9·0	1·19 (1·05-1·35)	0·96 (0·85-1·10)	0·95 (0·83-1·08)
	Items					
	Contacts (little vs. more)	9445	8·6	1·06 (0·97-1·16)	0·96 (0·87-1·05)	0·95 (0·86-1·04)
	Live alone (yes vs. no)	4505	9·4	1·16 (1·05-1·29)	1·01 (0·90-1·12)	1·00 (0·90-1·12)
Non-fatal myocardial infarction	Social isolation					

	Moderately vs. least	8046	5·5	1·08 (0·95-1·22)	0·99 (0·87-1·12)	0·97 (0·86-1·11)
	Most vs. least	3751	5·9	1·19 (1·02-1·38)	0·96 (0·82-1·13)	0·95 (0·81-1·11)
	Items					
	Contacts (little vs. more)	9483	5·6	1·07 (0·95-1·19)	0·96 (0·85-1·07)	0·95 (0·84-1·06)
	Live alone (yes vs. no)	4527	5·9	1·12 (0·98-1·27)	0·98 (0·85-1·12)	0·97 (0·85-1·11)
Non-fatal stroke	Social isolation					
	Moderately vs. least	8049	3·5	1·14 (0·97-1·33)	1·04 (0·89-1·22)	1·03 (0·88-1·21)
	Most vs. least	3754	3·7	1·22 (1·01-1·48)	0·98 (0·80-1·19)	0·96 (0·79-1·18)
	Items					
	Contacts (little vs. more)	9491	3·5	1·06 (0·92-1·22)	0·96 (0·83-1·10)	0·95 (0·82-1·09)
	Live alone (yes vs. no)	4525	4·1	1·25 (1·07-1·46)	1·06 (0·90-1·25)	1·07 (0·90-1·26)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 12. Sensitivity analyses of associations of loneliness and its items with subsequent risk for mortality, myocardial infarction, and stroke after excluding events occurring within the first two years

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Loneliness (yes vs. no)	1476	13.5	1.36 (1.19-1.55)	1.01 (0.88-1.16)	1.01 (0.88-1.16)
	Items					
	Lonely (yes vs. no)	4533	12.7	1.41 (1.29-1.54)	1.12 (1.02-1.24)	1.11 (1.01-1.22)
	Able to confide (never vs. usually)	3819	14.1	1.29 (1.18-1.40)	1.11 (1.01-1.21)	1.09 (0.99-1.19)
CVD mortality	Loneliness (yes vs. no)	1476	6.8	1.41 (1.16-1.69)	1.02 (0.84-1.24)	1.02 (0.84-1.24)
	Items					
	Lonely (yes vs. no)	4533	6.2	1.42 (1.26-1.61)	1.11 (0.97-1.27)	1.10 (0.96-1.25)
	Able to confide (never vs. usually)	3819	7.3	1.37 (1.21-1.55)	1.16 (1.02-1.32)	1.14 (1.00-1.29)
Overall						
Composites of incident myocardial infarction or stroke	Loneliness (yes vs. no)	1456	13.1	1.62 (1.41-1.87)	1.37 (1.19-1.59)	1.36 (1.17-1.57)
	Items					
	Lonely (yes vs. no)	4493	10.7	1.45 (1.32-1.60)	1.24 (1.12-1.38)	1.23 (1.10-1.36)
	Able to confide (never vs. usually)	3773	11.4	1.28 (1.15-1.41)	1.17 (1.06-1.30)	1.16 (1.05-1.29)
Incident myocardial infarction	Loneliness (yes vs. no)	1467	8.7	1.62 (1.36-1.92)	1.35 (1.13-1.61)	1.33 (1.11-1.59)
	Items					
	Lonely (yes vs. no)	4509	6.9	1.41 (1.25-1.59)	1.19 (1.04-1.35)	1.17 (1.03-1.33)

	Able to confide (never vs. usually)	3797	7.7	1.31 (1.16-1.48)	1.20 (1.06-1.36)	1.19 (1.05-1.35)
Incident stroke	Loneliness (yes vs. no)	1465	4.9	1.53 (1.22-1.92)	1.31 (1.04-1.65)	1.29 (1.03-1.63)
	Items					
	Lonely (yes vs. no)	4516	4.3	1.48 (1.27-1.73)	1.29 (1.10-1.52)	1.27 (1.08-1.50)
	Able to confide (never vs. usually)	3793	4.3	1.22 (1.03-1.43)	1.12 (0.95-1.32)	1.10 (0.93-1.30)
<hr/>						
Fatal events						
Composites of fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1476	1.0	1.76 (1.07-2.87)	1.27 (0.76-2.12)	1.28 (0.77-2.13)
	Items					
	Lonely (yes vs. no)	4533	0.8	1.64 (1.16-2.33)	1.31 (0.90-1.90)	1.28 (0.87-1.86)
	Able to confide (never vs. usually)	3819	1.0	1.60 (1.13-2.26)	1.34 (0.93-1.91)	1.31 (0.92-1.88)
Fatal myocardial infarction	Loneliness (yes vs. no)	1476	0.8	1.87 (1.09-3.21)	1.31 (0.75-2.30)	1.33 (0.76-2.33)
	Items					
	Lonely (yes vs. no)	4533	0.7	1.82 (1.24-2.69)	1.43 (0.94-2.17)	1.39 (0.92-2.12)
	Able to confide (never vs. usually)	3819	0.8	1.76 (1.20-2.59)	1.45 (0.98-2.16)	1.44 (0.97-2.14)
Fatal stroke	Loneliness (yes vs. no)	1476	0.2	1.32 (0.40-4.32)	1.09 (0.32-3.69)	1.08 (0.32-3.65)
	Items					
	Lonely (yes vs. no)	4533	0.1	1.04 (0.45-2.40)	0.88 (0.36-2.14)	0.87 (0.36-2.10)
	Able to confide (never vs. usually)	3819	0.2	1.02 (0.44-2.35)	0.91 (0.39-2.14)	0.88 (0.38-2.06)
<hr/>						
Non-fatal events						

Composites of non-fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1456	12.0	1.60 (1.39-1.86)	1.37 (1.18-1.60)	1.36 (1.17-1.58)
	Items					
	Lonely (yes vs. no)	4493	9.9	1.43 (1.29-1.59)	1.23 (1.11-1.38)	1.22 (1.09-1.36)
	Able to confide (never vs. usually)	3773	10.4	1.25 (1.13-1.39)	1.16 (1.04-1.29)	1.15 (1.03-1.28)
Non-fatal myocardial infarction	Loneliness (yes vs. no)	1467	7.8	1.59 (1.33-1.90)	1.34 (1.11-1.62)	1.33 (1.10-1.60)
	Items					
	Lonely (yes vs. no)	4509	6.2	1.37 (1.21-1.56)	1.16 (1.01-1.33)	1.15 (1.00-1.31)
	Able to confide (never vs. usually)	3797	6.9	1.27 (1.11-1.44)	1.17 (1.03-1.34)	1.16 (1.02-1.32)
Non-fatal stroke	Loneliness (yes vs. no)	1465	4.7	1.54 (1.23-1.94)	1.32 (1.05-1.68)	1.31 (1.03-1.66)
	Items					
	Lonely (yes vs. no)	4516	4.2	1.50 (1.28-1.76)	1.31 (1.11-1.55)	1.29 (1.09-1.53)
	Able to confide (never vs. usually)	3793	4.1	1.22 (1.04-1.44)	1.13 (0.95-1.33)	1.11 (0.94-1.32)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 13. Sensitivity analyses of associations of social isolation and its items with subsequent risk for mortality, myocardial infarction, and stroke in sample by censoring up to Dec 31, 2019 (this date was considered as the start of the COVID-19 pandemic in the UK)

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Social isolation					
	Moderately vs. least	8147	10.1	1.24 (1.12-1.37)	1.14 (1.03-1.27)	1.12 (1.01-1.24)
	Most vs. least	3804	13.3	1.71 (1.53-1.92)	1.37 (1.21-1.54)	1.33 (1.18-1.50)
	Items					
	Contacts (little vs. more)	9601	10.9	1.23 (1.13-1.35)	1.11 (1.01-1.21)	1.08 (0.99-1.18)
CVD mortality	Social isolation					
	Moderately vs. least	8147	5.0	1.34 (1.16-1.55)	1.21 (1.04-1.40)	1.18 (1.01-1.37)
	Most vs. least	3804	6.6	1.87 (1.58-2.20)	1.42 (1.20-1.70)	1.38 (1.16-1.65)
	Items					
	Contacts (little vs. more)	9601	5.4	1.31 (1.15-1.48)	1.14 (1.00-1.30)	1.10 (0.97-1.25)
	Live alone (yes vs. no)	4602	6.9	1.65 (1.45-1.89)	1.37 (1.19-1.58)	1.39 (1.21-1.60)
Overall						
Composites of incident myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8147	9.8	1.14 (1.03-1.27)	1.05 (0.94-1.16)	1.03 (0.93-1.15)
	Most vs. least	3804	10.9	1.31 (1.16-1.48)	1.06 (0.93-1.20)	1.04 (0.92-1.19)

	Items					
	Contacts (little vs. more)	9601	10.1	1.15 (1.05-1.26)	1.03 (0.94-1.13)	1.02 (0.93-1.12)
	Live alone (yes vs. no)	4602	11.0	1.22 (1.10-1.35)	1.05 (0.94-1.17)	1.05 (0.94-1.17)
Incident myocardial infarction	Social isolation					
	Moderately vs. least	8147	6.3	1.10 (0.97-1.24)	1.01 (0.89-1.14)	1.00 (0.88-1.13)
	Most vs. least	3804	7.1	1.26 (1.09-1.47)	1.03 (0.88-1.20)	1.01 (0.87-1.19)
	Items					
	Contacts (little vs. more)	9601	6.6	1.13 (1.01-1.26)	1.01 (0.90-1.13)	1.00 (0.89-1.12)
	Live alone (yes vs. no)	4602	6.9	1.15 (1.01-1.30)	1.01 (0.88-1.15)	1.00 (0.88-1.15)
Incident stroke	Social isolation					
	Moderately vs. least	8147	3.9	1.25 (1.06-1.47)	1.14 (0.97-1.34)	1.13 (0.96-1.33)
	Most vs. least	3804	4.2	1.40 (1.15-1.71)	1.13 (0.92-1.39)	1.11 (0.90-1.37)
	Items					
	Contacts (little vs. more)	9601	3.9	1.17 (1.01-1.35)	1.05 (0.91-1.22)	1.04 (0.89-1.20)
	Live alone (yes vs. no)	4602	4.7	1.35 (1.15-1.58)	1.16 (0.98-1.37)	1.16 (0.98-1.37)
<hr/>						
Fatal events						
Composites of fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8147	0.7	1.77 (1.16-2.70)	1.57 (1.02-2.42)	1.56 (1.01-2.40)
	Most vs. least	3804	1.2	3.02 (1.93-4.73)	2.25 (1.40-3.61)	2.24 (1.39-3.60)
	Items					

	Contacts (little vs. more)	9601	0.9	1.92 (1.36-2.72)	1.64 (1.15-2.35)	1.62 (1.13-2.32)
	Live alone (yes vs. no)	4602	1.1	1.97 (1.39-2.78)	1.58 (1.09-2.29)	1.59 (1.09-2.30)
Fatal myocardial infarction	Social isolation					
	Moderately vs. least	8147	0.5	1.60 (1.00-2.56)	1.42 (0.88-2.29)	1.42 (0.88-2.28)
	Most vs. least	3804	1.0	2.94 (1.80-4.80)	2.18 (1.30-3.66)	2.16 (1.28-3.63)
	Items					
	Contacts (little vs. more)	9601	0.7	1.87 (1.27-2.75)	1.60 (1.08-2.38)	1.58 (1.06-2.35)
	Live alone (yes vs. no)	4602	0.9	1.97 (1.34-2.89)	1.54 (1.02-2.33)	1.55 (1.02-2.35)
Fatal stroke	Social isolation					
	Moderately vs. least	8147	0.2	2.92 (1.06-8.03)	2.52 (0.91-6.99)	2.52 (0.91-7.01)
	Most vs. least	3804	0.2	3.48 (1.13-10.65)	2.53 (0.79-8.08)	2.62 (0.82-8.39)
	Items					
	Contacts (little vs. more)	9601	0.2	1.96 (0.90-4.25)	1.57 (0.71-3.47)	1.56 (0.70-3.46)
	Live alone (yes vs. no)	4602	0.2	2.18 (1.02-4.67)	1.94 (0.86-4.36)	2.03 (0.90-4.59)
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Non-fatal events						
Composites of non-fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8147	9.1	1.11 (1.00-1.24)	1.02 (0.92-1.14)	1.01 (0.91-1.13)
	Most vs. least	3804	9.6	1.22 (1.07-1.39)	0.99 (0.86-1.13)	0.98 (0.85-1.12)
	Items					
	Contacts (little vs. more)	9601	9.2	1.11 (1.01-1.22)	1.00 (0.90-1.10)	0.99 (0.90-1.09)
	Live alone (yes vs. no)	4602	9.9	1.16 (1.04-1.29)	1.01 (0.90-1.13)	1.01 (0.90-1.13)

Non-fatal myocardial infarction	Social isolation					
	Moderately vs. least	8147	5.8	1.06 (0.93-1.21)	0.98 (0.86-1.12)	0.97 (0.85-1.11)
	Most vs. least	3804	6.1	1.16 (0.99-1.36)	0.95 (0.80-1.12)	0.94 (0.79-1.11)
	Items					
	Contacts (little vs. more)	9601	5.9	1.07 (0.96-1.21)	0.97 (0.86-1.09)	0.96 (0.85-1.08)
	Live alone (yes vs. no)	4602	6.0	1.08 (0.95-1.24)	0.96 (0.83-1.10)	0.96 (0.83-1.10)
Non-fatal stroke	Social isolation					
	Moderately vs. least	8147	3.8	1.21 (1.03-1.43)	1.11 (0.94-1.31)	1.10 (0.93-1.30)
	Most vs. least	3804	4.0	1.36 (1.12-1.67)	1.10 (0.89-1.35)	1.08 (0.87-1.33)
	Items					
	Contacts (little vs. more)	9601	3.7	1.15 (0.99-1.33)	1.04 (0.89-1.20)	1.02 (0.88-1.18)
	Live alone (yes vs. no)	4602	4.4	1.32 (1.13-1.56)	1.13 (0.96-1.34)	1.14 (0.96-1.35)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 14. Sensitivity analyses of associations of loneliness and its items with subsequent risk for mortality, myocardial infarction, and stroke in sample by censoring up to Dec 31, 2019 (this date was considered as the start of the COVID-19 pandemic in the UK)

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Loneliness (yes vs. no)	1487	12.5	1.39 (1.20-1.61)	1.04 (0.89-1.21)	1.04 (0.89-1.21)
	Items					
	Lonely (yes vs. no)	4570	11.5	1.42 (1.28-1.56)	1.14 (1.02-1.26)	1.13 (1.01-1.25)
	Able to confide (never vs. usually)	3849	12.8	1.30 (1.18-1.44)	1.12 (1.01-1.24)	1.10 (0.99-1.22)
CVD mortality	Loneliness (yes vs. no)	1487	6.4	1.48 (1.20-1.82)	1.10 (0.89-1.37)	1.11 (0.90-1.38)
	Items					
	Lonely (yes vs. no)	4570	5.5	1.42 (1.23-1.64)	1.14 (0.98-1.33)	1.13 (0.97-1.32)
	Able to confide (never vs. usually)	3849	6.7	1.44 (1.25-1.66)	1.23 (1.06-1.42)	1.21 (1.05-1.40)
Overall						
Composites of incident myocardial infarction or stroke	Loneliness (yes vs. no)	1487	14.4	1.70 (1.47-1.96)	1.44 (1.24-1.67)	1.42 (1.23-1.65)
	Items					
	Lonely (yes vs. no)	4570	11.2	1.43 (1.29-1.59)	1.23 (1.11-1.38)	1.22 (1.09-1.36)
	Able to confide (never vs. usually)	3849	12.5	1.34 (1.21-1.49)	1.23 (1.11-1.37)	1.22 (1.10-1.36)
Incident myocardial infarction	Loneliness (yes vs. no)	1487	9.7	1.74 (1.46-2.06)	1.47 (1.23-1.76)	1.45 (1.21-1.74)
	Items					
	Lonely (yes vs. no)	4570	7.4	1.45 (1.27-1.64)	1.25 (1.09-1.43)	1.23 (1.07-1.41)

	Able to confide (never vs. usually)	3849	8.3	1.34 (1.18-1.53)	1.23 (1.08-1.41)	1.22 (1.07-1.39)
Incident stroke	Loneliness (yes vs. no)	1487	4.9	1.47 (1.16-1.87)	1.22 (0.95-1.57)	1.21 (0.94-1.55)
	Items					
	Lonely (yes vs. no)	4570	4.2	1.37 (1.16-1.62)	1.16 (0.98-1.38)	1.14 (0.96-1.36)
	Able to confide (never vs. usually)	3849	4.6	1.27 (1.07-1.50)	1.15 (0.97-1.36)	1.13 (0.96-1.35)
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	Fatal events					
Composites of fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1487	1.2	2.07 (1.27-3.36)	1.51 (0.91-2.50)	1.52 (0.91-2.51)
	Items					
	Lonely (yes vs. no)	4570	0.9	1.81 (1.26-2.61)	1.47 (0.99-2.16)	1.42 (0.96-2.10)
	Able to confide (never vs. usually)	3849	1.1	1.67 (1.16-2.41)	1.36 (0.93-1.97)	1.33 (0.92-1.94)
Fatal myocardial infarction	Loneliness (yes vs. no)	1487	1.1	2.35 (1.40-3.95)	1.70 (0.99-2.93)	1.72 (1.00-2.96)
	Items					
	Lonely (yes vs. no)	4570	0.8	1.87 (1.25-2.79)	1.49 (0.97-2.30)	1.44 (0.93-2.22)
	Able to confide (never vs. usually)	3849	0.9	1.91 (1.29-2.83)	1.54 (1.02-2.32)	1.53 (1.02-2.30)
Fatal Stroke	Loneliness (yes vs. no)	1487	0.1	0.99 (0.23-4.18)	0.76 (0.18-3.32)	0.75 (0.17-3.29)
	Items					
	Lonely (yes vs. no)	4570	0.2	1.55 (0.68-3.56)	1.31 (0.54-3.17)	1.29 (0.53-3.12)
	Able to confide (never vs. usually)	3849	0.1	0.83 (0.32-2.20)	0.70 (0.26-1.87)	0.67 (0.25-1.80)
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	Non-fatal events					
Composites of non-fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1487	13.1	1.66 (1.43-1.93)	1.43 (1.22-1.67)	1.41 (1.21-1.65)

	Items					
	Lonely (yes vs. no)	4570	10.2	1.40 (1.26-1.56)	1.21 (1.08-1.36)	1.20 (1.07-1.34)
	Able to confide (never vs. usually)	3849	11.4	1.32 (1.18-1.47)	1.22 (1.09-1.36)	1.21 (1.08-1.35)
Non-fatal myocardial infarction	Loneliness (yes vs. no)	1487	8.6	1.67 (1.39-2.01)	1.44 (1.19-1.74)	1.42 (1.17-1.72)
	Items					
	Lonely (yes vs. no)	4570	6.6	1.41 (1.23-1.61)	1.22 (1.06-1.41)	1.21 (1.05-1.39)
	Able to confide (never vs. usually)	3849	7.3	1.29 (1.13-1.48)	1.20 (1.05-1.38)	1.19 (1.04-1.37)
Non-fatal stroke	Loneliness (yes vs. no)	1487	4.8	1.49 (1.17-1.90)	1.25 (0.97-1.60)	1.23 (0.96-1.59)
	Items					
	Lonely (yes vs. no)	4570	4.1	1.36 (1.15-1.61)	1.16 (0.97-1.38)	1.14 (0.95-1.36)
	Able to confide (never vs. usually)	3849	4.5	1.29 (1.08-1.53)	1.17 (0.98-1.40)	1.16 (0.97-1.38)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 15. Sensitivity analyses of associations of social isolation and its items with subsequent risk for mortality, myocardial infarction, and stroke with follow-up of six years

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Social isolation					
	Moderately vs. least	8147	6.4	1.24 (1.05-1.47)	1.12 (0.94-1.33)	1.10 (0.93-1.31)
	Most vs. least	3804	8.4	1.69 (1.39-2.05)	1.28 (1.04-1.57)	1.25 (1.02-1.54)
	Items					
	Contacts (little vs. more)	9601	6.7	1.17 (1.02-1.36)	1.03 (0.88-1.19)	1.00 (0.86-1.17)
	Live alone (yes vs. no)	4602	8.9	1.62 (1.39-1.89)	1.32 (1.12-1.56)	1.32 (1.12-1.56)
CVD mortality	Social isolation					
	Moderately vs. least	8147	3.1	1.44 (1.12-1.86)	1.24 (0.96-1.61)	1.21 (0.94-1.57)
	Most vs. least	3804	4.1	1.94 (1.46-2.58)	1.31 (0.97-1.77)	1.27 (0.94-1.72)
	Items					
	Contacts (little vs. more)	9601	3.2	1.26 (1.02-1.56)	1.04 (0.83-1.30)	1.01 (0.81-1.26)
	Live alone (yes vs. no)	4602	4.3	1.71 (1.37-2.14)	1.29 (1.02-1.64)	1.30 (1.02-1.66)
Overall						
Composites of incident myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8147	7.4	1.20 (1.03-1.41)	1.08 (0.92-1.27)	1.07 (0.91-1.25)
	Most vs. least	3804	8.5	1.42 (1.18-1.71)	1.10 (0.91-1.34)	1.09 (0.89-1.32)

	Items					
	Contacts (little vs. more)	9601	7.8	1.22 (1.06-1.40)	1.08 (0.93-1.24)	1.06 (0.92-1.22)
	Live alone (yes vs. no)	4602	8.3	1.22 (1.05-1.43)	1.01 (0.86-1.19)	1.02 (0.87-1.20)
Incident myocardial infarction	Social isolation					
	Moderately vs. least	8147	4.7	1.11 (0.91-1.34)	1.01 (0.83-1.23)	1.00 (0.82-1.22)
	Most vs. least	3804	5.1	1.22 (0.97-1.54)	0.97 (0.76-1.24)	0.95 (0.74-1.22)
	Items					
	Contacts (little vs. more)	9601	4.8	1.11 (0.93-1.31)	0.99 (0.83-1.18)	0.97 (0.82-1.16)
	Live alone (yes vs. no)	4602	4.9	1.10 (0.90-1.34)	0.93 (0.75-1.15)	0.94 (0.76-1.15)
Incident stroke	Social isolation					
	Moderately vs. least	8147	3.0	1.42 (1.09-1.83)	1.25 (0.96-1.62)	1.23 (0.94-1.59)
	Most vs. least	3804	3.7	1.84 (1.37-2.47)	1.36 (1.00-1.86)	1.34 (0.98-1.82)
	Items					
	Contacts (little vs. more)	9601	3.2	1.35 (1.08-1.68)	1.16 (0.93-1.46)	1.13 (0.90-1.42)
	Live alone (yes vs. no)	4602	3.9	1.59 (1.26-2.01)	1.28 (1.00-1.63)	1.29 (1.01-1.65)
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Fatal events						
Composites of fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8147	0.5	1.95 (1.00-3.80)	1.75 (0.89-3.44)	1.71 (0.87-3.37)
	Most vs. least	3804	1.0	3.66 (1.84-7.27)	2.78 (1.34-5.76)	2.77 (1.33-5.76)
	Items					

	Contacts (little vs. more)	9601	0.7	2.07 (1.22-3.52)	1.77 (1.02-3.05)	1.74 (1.01-3.00)
	Live alone (yes vs. no)	4602	0.9	2.17 (1.30-3.63)	1.73 (0.99-3.01)	1.76 (1.01-3.07)
Fatal myocardial infarction	Social isolation					
	Moderately vs. least	8147	0.4	2.07 (0.97-4.40)	1.89 (0.88-4.06)	1.89 (0.88-4.06)
	Most vs. least	3804	0.7	3.54 (1.60-7.81)	2.74 (1.18-6.33)	2.75 (1.19-6.40)
	Items					
	Contacts (little vs. more)	9601	0.5	2.15 (1.17-3.94)	1.85 (0.99-3.44)	1.83 (0.98-3.41)
	Live alone (yes vs. no)	4602	0.6	1.89 (1.04-3.42)	1.52 (0.80-2.89)	1.56 (0.82-2.96)
Fatal stroke	Social isolation					
	Moderately vs. least	8147	0.1	1.58 (0.38-6.60)	1.34 (0.31-5.74)	1.31 (0.30-5.64)
	Most vs. least	3804	0.3	4.01 (1.00-16.13)	2.81 (0.64-12.33)	2.81 (0.63-12.49)
	Items					
	Contacts (little vs. more)	9601	0.2	1.84 (0.62-5.52)	1.53 (0.49-4.76)	1.46 (0.47-4.60)
	Live alone (yes vs. no)	4602	0.3	3.37 (1.18-9.61)	2.59 (0.83-8.05)	2.78 (0.89-8.71)
<hr/>						
Non-fatal events						
Composites of non-fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	8147	6.8	1.17 (0.99-1.37)	1.05 (0.89-1.24)	1.04 (0.88-1.23)
	Most vs. least	3804	7.5	1.32 (1.08-1.60)	1.02 (0.83-1.25)	1.01 (0.82-1.24)
	Items					
	Contacts (little vs. more)	9601	7.1	1.17 (1.01-1.35)	1.04 (0.90-1.20)	1.02 (0.88-1.18)
	Live alone (yes vs. no)	4602	7.4	1.16 (0.99-1.37)	0.96 (0.81-1.14)	0.97 (0.82-1.16)

Non-fatal myocardial infarction	Social isolation					
	Moderately vs. least	8147	4.2	1.06 (0.87-1.29)	0.97 (0.79-1.19)	0.96 (0.78-1.17)
	Most vs. least	3804	4.3	1.10 (0.86-1.41)	0.87 (0.67-1.13)	0.86 (0.66-1.12)
	Items					
	Contacts (little vs. more)	9601	4.2	1.04 (0.87-1.24)	0.93 (0.78-1.12)	0.92 (0.76-1.10)
	Live alone (yes vs. no)	4602	4.3	1.03 (0.84-1.28)	0.88 (0.71-1.10)	0.89 (0.71-1.11)
Non-fatal stroke	Social isolation					
	Moderately vs. least	8147	2.9	1.41 (1.08-1.84)	1.24 (0.95-1.62)	1.22 (0.94-1.60)
	Most vs. least	3804	3.5	1.77 (1.31-2.39)	1.31 (0.95-1.80)	1.28 (0.93-1.76)
	Items					
	Contacts (little vs. more)	9601	3.0	1.33 (1.06-1.67)	1.15 (0.91-1.45)	1.12 (0.89-1.41)
	Live alone (yes vs. no)	4602	3.7	1.53 (1.21-1.95)	1.23 (0.95-1.59)	1.25 (0.97-1.61)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 16. Sensitivity analyses of associations of social isolation and its items with subsequent risk for mortality, myocardial infarction, and stroke excluding the events occurring in the first six years

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Social isolation					
	Moderately vs. least	7841	17.8	1.29 (1.17-1.43)	1.19 (1.08-1.32)	1.18 (1.07-1.31)
	Most vs. least	3616	22.2	1.71 (1.52-1.91)	1.39 (1.23-1.57)	1.35 (1.20-1.53)
	Items					
	Contacts (little vs. more)	9220	16.1	1.28 (1.17-1.40)	1.17 (1.07-1.27)	1.14 (1.04-1.25)
	Live alone (yes vs. no)	4362	23.5	1.53 (1.39-1.68)	1.29 (1.17-1.43)	1.30 (1.18-1.44)
CVD mortality	Social isolation					
	Moderately vs. least	7841	8.9	1.37 (1.19-1.58)	1.25 (1.08-1.45)	1.23 (1.06-1.42)
	Most vs. least	3616	11.3	1.83 (1.55-2.15)	1.45 (1.22-1.72)	1.40 (1.18-1.67)
	Items					
	Contacts (little vs. more)	9220	9.6	1.36 (1.20-1.53)	1.21 (1.07-1.37)	1.17 (1.03-1.33)
	Live alone (yes vs. no)	4362	12.0	1.62 (1.42-1.85)	1.38 (1.20-1.59)	1.40 (1.22-1.61)
Overall						
Composites of incident myocardial infarction or stroke	Social isolation					
	Moderately vs. least	7559	12.9	1.07 (0.96-1.21)	0.99 (0.88-1.11)	0.98 (0.87-1.10)
	Most vs. least	3472	13.7	1.17 (1.02-1.35)	0.96 (0.82-1.11)	0.94 (0.81-1.10)

	Items					
	Contacts (little vs. more)	8874	12.7	1.03 (0.93-1.14)	0.93 (0.84-1.03)	0.92 (0.83-1.03)
	Live alone (yes vs. no)	4200	14.9	1.22 (1.09-1.37)	1.08 (0.95-1.22)	1.07 (0.95-1.21)
Incident myocardial infarction	Social isolation					
	Moderately vs. least	7661	8.3	1.08 (0.93-1.24)	0.98 (0.85-1.14)	0.98 (0.85-1.13)
	Most vs. least	3527	9.7	1.29 (1.08-1.52)	1.05 (0.88-1.25)	1.03 (0.86-1.24)
	Items					
	Contacts (little vs. more)	9004	8.6	1.09 (0.96-1.24)	0.97 (0.86-1.11)	0.97 (0.85-1.10)
	Live alone (yes vs. no)	4260	9.7	1.23 (1.06-1.42)	1.09 (0.94-1.27)	1.08 (0.93-1.25)
Incident stroke	Social isolation					
	Moderately vs. least	7728	5.2	1.06 (0.89-1.27)	0.99 (0.82-1.18)	0.98 (0.82-1.17)
	Most vs. least	3554	4.8	1.00 (0.80-1.26)	0.83 (0.65-1.05)	0.82 (0.64-1.04)
	Items					
	Contacts (little vs. more)	9078	4.9	0.96 (0.82-1.13)	0.89 (0.75-1.05)	0.88 (0.74-1.04)
	Live alone (yes vs. no)	4290	5.7	1.14 (0.95-1.37)	1.00 (0.82-1.21)	1.00 (0.82-1.22)
<hr/>						
Fatal events						
Composites of fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	7841	0.9	1.35 (0.86-2.11)	1.19 (0.75-1.88)	1.19 (0.75-1.87)
	Most vs. least	3616	1.4	2.11 (1.29-3.45)	1.55 (0.92-2.62)	1.54 (0.91-2.60)
	Items					

	Contacts (little vs. more)	9220	1.0	1.40 (0.95-2.04)	1.19 (0.81-1.75)	1.18 (0.80-1.74)
	Live alone (yes vs. no)	4362	1.4	1.87 (1.26-2.77)	1.53 (1.00-2.33)	1.52 (0.99-2.32)
Fatal myocardial infarction	Social isolation					
	Moderately vs. least	7841	0.6	1.16 (0.70-1.94)	1.03 (0.61-1.74)	1.04 (0.62-1.74)
	Most vs. least	3616	1.2	2.29 (1.35-3.90)	1.68 (0.96-2.95)	1.66 (0.94-2.93)
	Items					
	Contacts (little vs. more)	9220	0.8	1.33 (0.87-2.04)	1.14 (0.74-1.76)	1.13 (0.73-1.75)
	Live alone (yes vs. no)	4362	1.2	2.14 (1.38-3.30)	1.71 (1.07-2.73)	1.70 (1.06-2.72)
Fatal stroke	Social isolation					
	Moderately vs. least	7841	0.3	2.36 (0.91-6.15)	2.09 (0.79-5.52)	2.06 (0.78-5.46)
	Most vs. least	3616	0.1	1.20 (0.30-4.81)	0.88 (0.21-3.69)	0.87 (0.21-3.68)
	Items					
	Contacts (little vs. more)	9220	0.2	1.51 (0.66-3.45)	1.24 (0.53-2.88)	1.22 (0.52-2.86)
	Live alone (yes vs. no)	4362	0.2	1.22 (0.48-3.11)	1.11 (0.41-2.97)	1.08 (0.40-2.92)
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Non-fatal events						
Composites of non-fatal myocardial infarction or stroke	Social isolation					
	Moderately vs. least	7559	12.0	1.06 (0.94-1.19)	0.98 (0.87-1.10)	0.97 (0.86-1.09)
	Most vs. least	3472	12.3	1.12 (0.96-1.30)	0.92 (0.79-1.07)	0.90 (0.77-1.06)
	Items					
	Contacts (little vs. more)	8874	11.7	1.01 (0.91-1.13)	0.92 (0.82-1.02)	0.91 (0.81-1.01)
	Live alone (yes vs. no)	4200	13.4	1.17 (1.04-1.33)	1.04 (0.92-1.19)	1.03 (0.91-1.18)

Non-fatal myocardial infarction	Social isolation					
	Moderately vs. least	7661	7.6	1.07 (0.92-1.24)	0.98 (0.85-1.14)	0.97 (0.84-1.13)
	Most vs. least	3527	8.4	1.20 (1.00-1.44)	0.99 (0.82-1.20)	0.98 (0.81-1.18)
	Items					
	Contacts (little vs. more)	9004	7.8	1.07 (0.93-1.22)	0.96 (0.84-1.10)	0.95 (0.83-1.09)
	Live alone (yes vs. no)	4260	8.5	1.15 (0.99-1.34)	1.04 (0.88-1.21)	1.02 (0.87-1.20)
Non-fatal stroke	Social isolation					
	Moderately vs. least	7728	5.0	1.03 (0.86-1.23)	0.96 (0.80-1.15)	0.95 (0.79-1.14)
	Most vs. least	3554	4.6	1.00 (0.79-1.26)	0.83 (0.65-1.05)	0.81 (0.64-1.04)
	Items					
	Contacts (little vs. more)	9078	4.6	0.95 (0.80-1.12)	0.87 (0.74-1.03)	0.86 (0.73-1.02)
	Live alone (yes vs. no)	4290	5.4	1.14 (0.94-1.37)	0.99 (0.82-1.21)	1.00 (0.82-1.21)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 17. Sensitivity analyses of associations of loneliness and its items with subsequent risk for mortality, myocardial infarction, and stroke with follow-up of six years

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Loneliness (yes vs. no)	1487	9.3	1.65 (1.31-2.09)	1.21 (0.95-1.54)	1.22 (0.96-1.55)
	Items					
	Lonely (yes vs. no)	4570	7.5	1.49 (1.26-1.75)	1.15 (0.97-1.38)	1.15 (0.96-1.37)
	Able to confide (never vs. usually)	3849	8.5	1.40 (1.19-1.65)	1.19 (1.01-1.41)	1.18 (0.99-1.40)
CVD mortality	Loneliness (yes vs. no)	1487	4.9	1.92 (1.39-2.64)	1.38 (0.99-1.92)	1.42 (1.02-1.99)
	Items					
	Lonely (yes vs. no)	4570	3.5	1.51 (1.19-1.92)	1.15 (0.89-1.48)	1.15 (0.89-1.49)
	Able to confide (never vs. usually)	3849	4.6	1.71 (1.36-2.16)	1.43 (1.12-1.81)	1.42 (1.12-1.80)
Overall						
Composites of incident myocardial infarction or stroke	Loneliness (yes vs. no)	1487	11.0	1.73 (1.39-2.14)	1.39 (1.11-1.73)	1.38 (1.11-1.73)
	Items					
	Lonely (yes vs. no)	4570	8.6	1.51 (1.29-1.76)	1.25 (1.06-1.47)	1.23 (1.04-1.45)
	Able to confide (never vs. usually)	3849	9.5	1.35 (1.15-1.58)	1.20 (1.02-1.41)	1.19 (1.01-1.40)
Incident myocardial infarction	Loneliness (yes vs. no)	1487	7.5	1.85 (1.43-2.40)	1.53 (1.17-2.00)	1.53 (1.16-2.00)
	Items					
	Lonely (yes vs. no)	4570	5.5	1.49 (1.23-1.81)	1.26 (1.03-1.56)	1.26 (1.02-1.54)

	Able to confide (never vs. usually)	3849	6.3	1.41 (1.16-1.71)	1.28 (1.05-1.56)	1.26 (1.04-1.54)
Incident stroke	Loneliness (yes vs. no)	1487	3.9	1.58 (1.11-2.26)	1.18 (0.82-1.71)	1.18 (0.82-1.71)
	Items					
	Lonely (yes vs. no)	4570	3.5	1.61 (1.27-2.06)	1.27 (0.98-1.65)	1.24 (0.96-1.61)
	Able to confide (never vs. usually)	3849	3.4	1.25 (0.97-1.62)	1.06 (0.81-1.37)	1.05 (0.81-1.36)
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	Fatal events					
Composites of fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1487	0.9	2.01 (0.95-4.24)	1.37 (0.63-2.98)	1.38 (0.63-3.02)
	Items					
	Lonely (yes vs. no)	4570	0.8	2.09 (1.22-3.56)	1.60 (0.90-2.84)	1.57 (0.88-2.80)
	Able to confide (never vs. usually)	3849	1.0	2.37 (1.41-3.98)	1.86 (1.09-3.18)	1.82 (1.07-3.12)
Fatal myocardial infarction	Loneliness (yes vs. no)	1487	0.8	2.40 (1.07-5.38)	1.65 (0.71-3.86)	1.67 (0.71-3.91)
	Items					
	Lonely (yes vs. no)	4570	0.6	1.91 (1.02-3.54)	1.44 (0.74-2.82)	1.43 (0.73-2.78)
	Able to confide (never vs. usually)	3849	0.9	3.19 (1.79-5.69)	2.57 (1.42-4.67)	2.51 (1.38-4.56)
Fatal Stroke	Loneliness (yes vs. no)	1487	0.1	0.94 (0.12-7.19)	0.60 (0.08-4.80)	0.56 (0.07-4.55)
	Items					
	Lonely (yes vs. no)	4570	0.2	2.78 (0.95-8.14)	2.17 (0.69-6.89)	2.17 (0.67-6.99)
	Able to confide (never vs. usually)	3849	0.1	0.63 (0.14-2.82)	0.45 (0.10-2.07)	0.44 (0.09-2.03)
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	Non-fatal events					

Composites of non-fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1487	10.1	1.70 (1.36-2.13)	1.39 (1.10-1.75)	1.38 (1.09-1.74)
	Items					
	Lonely (yes vs. no)	4570	7.8	1.46 (1.25-1.72)	1.22 (1.02-1.45)	1.20 (1.01-1.43)
Non-fatal myocardial infarction	Able to confide (never vs. usually)	3849	8.4	1.28 (1.09-1.51)	1.15 (0.97-1.36)	1.14 (0.96-1.35)
	Loneliness (yes vs. no)	1487	6.7	1.80 (1.37-2.37)	1.51 (1.14-2.01)	1.51 (1.13-2.01)
	Items					
Non-fatal stroke	Lonely (yes vs. no)	4570	4.9	1.45 (1.19-1.78)	1.24 (1.00-1.55)	1.24 (0.99-1.54)
	Able to confide (never vs. usually)	3849	5.4	1.28 (1.04-1.58)	1.18 (0.95-1.45)	1.16 (0.94-1.44)
	Loneliness (yes vs. no)	1487	3.8	1.61 (1.12-2.32)	1.22 (0.84-1.77)	1.22 (0.84-1.77)
Non-fatal stroke	Items					
	Lonely (yes vs. no)	4570	3.3	1.57 (1.22-2.01)	1.24 (0.95-1.62)	1.21 (0.93-1.58)
	Able to confide (never vs. usually)	3849	3.3	1.28 (0.99-1.67)	1.09 (0.84-1.43)	1.09 (0.83-1.42)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 18. Sensitivity analyses of associations of loneliness and its items with subsequent risk for mortality, myocardial infarction, and stroke excluding the events occurring in the first six years

Outcomes	Exposures	N	Incident rate (per 1000 person-years)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Mortality						
All-cause mortality	Loneliness (yes vs. no)	1406	18.8	1.23 (1.05-1.44)	0.92 (0.78-1.08)	0.92 (0.78-1.08)
	Items					
	Lonely (yes vs. no)	4368	19.0	1.37 (1.24-1.52)	1.10 (0.99-1.23)	1.09 (0.98-1.22)
	Able to confide (never vs. usually)	3656	20.7	1.22 (1.10-1.35)	1.05 (0.95-1.17)	1.04 (0.94-1.15)
CVD mortality	Loneliness (yes vs. no)	1406	9.4	1.24 (0.99-1.55)	0.91 (0.72-1.14)	0.91 (0.72-1.14)
	Items					
	Lonely (yes vs. no)	4368	9.3	1.37 (1.19-1.58)	1.08 (0.92-1.25)	1.06 (0.91-1.23)
	Able to confide (never vs. usually)	3656	10.5	1.24 (1.08-1.44)	1.06 (0.91-1.23)	1.04 (0.90-1.20)
Overall						
Composites of incident myocardial infarction or stroke	Loneliness (yes vs. no)	1332	18.1	1.58 (1.33-1.88)	1.38 (1.16-1.65)	1.36 (1.14-1.62)
	Items					
	Lonely (yes vs. no)	4192	14.7	1.39 (1.24-1.57)	1.23 (1.08-1.39)	1.20 (1.06-1.37)
	Able to confide (never vs. usually)	3492	15.8	1.25 (1.11-1.42)	1.17 (1.04-1.33)	1.16 (1.03-1.32)
Incident myocardial infarction	Loneliness (yes vs. no)	1352	11.1	1.47 (1.18-1.81)	1.23 (0.99-1.54)	1.22 (0.98-1.51)
	Items					
	Lonely (yes vs. no)	4246	9.4	1.36 (1.18-1.57)	1.16 (0.99-1.35)	1.14 (0.97-1.33)

	Able to confide (never vs. usually)	3548	10.4	1.24 (1.07-1.44)	1.15 (0.99-1.34)	1.14 (0.98-1.32)
Incident stroke	Loneliness (yes vs. no)	1382	7.2	1.59 (1.22-2.06)	1.46 (1.11-1.91)	1.43 (1.09-1.87)
	Items					
	Lonely (yes vs. no)	4305	5.8	1.35 (1.12-1.63)	1.25 (1.02-1.52)	1.23 (1.01-1.49)
	Able to confide (never vs. usually)	3594	6.3	1.27 (1.05-1.54)	1.22 (1.00-1.48)	1.20 (0.99-1.46)
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	Fatal events					
Composites of fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1406	1.3	1.65 (0.90-3.00)	1.23 (0.66-2.29)	1.21 (0.65-2.25)
	Items					
	Lonely (yes vs. no)	4368	1.0	1.46 (0.95-2.25)	1.17 (0.74-1.85)	1.13 (0.71-1.80)
	Able to confide (never vs. usually)	3656	1.2	1.28 (0.83-1.97)	1.08 (0.69-1.69)	1.05 (0.67-1.64)
Fatal myocardial infarction	Loneliness (yes vs. no)	1406	1.1	1.70 (0.88-3.29)	1.23 (0.62-2.44)	1.22 (0.62-2.41)
	Items					
	Lonely (yes vs. no)	4368	0.9	1.71 (1.07-2.72)	1.34 (0.81-2.21)	1.30 (0.79-2.15)
	Able to confide (never vs. usually)	3656	0.9	1.30 (0.80-2.12)	1.08 (0.66-1.77)	1.06 (0.65-1.75)
Fatal Stroke	Loneliness (yes vs. no)	1406	0.2	1.37 (0.32-5.85)	1.26 (0.28-5.61)	1.21 (0.27-5.43)
	Items					
	Lonely (yes vs. no)	4368	0.1	0.63 (0.19-2.15)	0.55 (0.15-1.95)	0.53 (0.15-1.89)
	Able to confide (never vs. usually)	3656	0.2	1.10 (0.41-2.98)	1.07 (0.39-2.95)	1.02 (0.37-2.81)
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	Non-fatal events					

Composites of non-fatal myocardial infarction or stroke	Loneliness (yes vs. no)	1332	16.6	1.56 (1.31-1.87)	1.38 (1.15-1.66)	1.36 (1.13-1.63)
	Items					
	Lonely (yes vs. no)	4192	13.6	1.38 (1.22-1.56)	1.22 (1.07-1.39)	1.20 (1.05-1.37)
	Able to confide (never vs. usually)	3492	14.6	1.26 (1.11-1.42)	1.18 (1.04-1.35)	1.17 (1.03-1.34)
Non-fatal myocardial infarction	Loneliness (yes vs. no)	1352	10.0	1.44 (1.15-1.80)	1.23 (0.97-1.55)	1.21 (0.96-1.52)
	Items					
	Lonely (yes vs. no)	4246	8.4	1.33 (1.14-1.55)	1.14 (0.97-1.34)	1.12 (0.95-1.32)
	Able to confide (never vs. usually)	3548	9.4	1.24 (1.06-1.45)	1.15 (0.98-1.35)	1.14 (0.98-1.34)
Non-fatal stroke	Loneliness (yes vs. no)	1382	7.0	1.60 (1.22-2.08)	1.48 (1.12-1.94)	1.45 (1.10-1.91)
	Items					
	Lonely (yes vs. no)	4305	5.7	1.38 (1.15-1.67)	1.28 (1.05-1.56)	1.26 (1.03-1.54)
	Able to confide (never vs. usually)	3594	6.0	1.28 (1.06-1.55)	1.23 (1.01-1.50)	1.21 (1.00-1.48)

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 19. Proportion of mediation analysis for the association between social isolation, loneliness, and subsequent risk of mortality and MACE

Mediators	Social isolation			Loneliness	
	All-cause mortality	CVD mortality	Composites of fatal myocardial infarction or stroke	Composites of incident myocardial infarction or stroke	Composites of non-fatal myocardial infarction or stroke
	Mediating proportion (95%CI)*, %	Mediating proportion (95%CI)*, %	Mediating proportion (95%CI)*, %	Mediating proportion (95%CI)*, %	Mediating proportion (95%CI)*, %
Behavioural factors					
Smoking status	5.9 (3.7, 8.9)	4.2 (2.4, 6.9)	3.1 (0.8, 8.2)	2.6 (1.1, 5.1)	2.7 (1.1, 5.6)
Alcohol consumption status	4.3 (1.9, 7.3)	6.4 (3.5, 10.5)	4.7 (0.3, 11.7)	2.7 (1.1, 4.9)	2.7 (0.9, 5.5)
Physical activity (MET Score)	10.6 (7.2, 15.2)	12.7 (8.4, 19.2)	9.9 (4.0, 23.3)	4.2 (1.7, 8.0)	3.5 (0.9, 7.2)
TV watching time	5.9 (3.7, 9.1)	6.0 (3.1, 9.8)	2.5 (-2.3, 9.1)	3.8 (1.1, 7.7)	3.9 (0.7, 8.2)
Healthy diet score	0.8 (-0.1, 1.8)	0.7 (-0.4, 2.1)	NA	1.7 (-0.3, 4.3)	2.1 (-0.6, 5.3)
Sleep duration	2.1 (1.1, 3.8)	2.1 (0.9, 4.0)	0.5 (-1.1, 2.7)	6.6 (3.6, 11.2)	7.5 (4.2, 13.0)
All significant behavioural factors	26.0 (19.5, 35.6)	28.2 (20.3, 43.0)	17.8 (8.9, 39.5)	17.6 (11.7, 28.3)	17.8 (11.3, 30.7)
Psychological factors					
Anxiety	0.2 (-0.2, 0.6)	0.3 (-0.1, 1.0)	0.1 (-0.6, 1.0)	0.3 (-0.3, 1.3)	0.4 (-0.3, 1.4)
Depression	2.1 (0.9, 3.5)	1.6 (0.4, 3.5)	1.9 (-0.5, 6.2)	2.4 (0.4, 5.5)	2.2 (-0.2, 5.6)
Ever seeking help from physicians due to anxiety or depressive symptoms	0.2 (-1.4, 1.6)	NA	NA	4.7 (-0.5, 11.4)	5.8 (0.2, 13.2)
All significant psychological factors	NA	NA	NA	NA	NA
Physiological factors					
Body mass index	2.1 (1.1, 3.6)	3.0 (1.5, 5.7)	0.2 (-1.8, 2.1)	2.5 (1.1, 4.8)	2.8 (1.1, 5.7)

Grip strength	4.3 (2.7, 6.7)	4.6 (2.6, 7.3)	1.2 (-1.0, 4.4)	6.2 (3.4, 11.0)	6.7 (3.5, 11.9)
Systolic blood pressure	NA	NA	NA	NA	NA
Diastolic blood pressure	0.0 (-0.6, 0.7)	0.0 (-0.6, 0.7)	0.0 (-0.6, 0.8)	0.0 (-0.6, 0.5)	-0.1 (-0.7, 0.4)
Hyperlipidaemia	NA	NA	0.0 (-0.6, 0.5)	0.7 (-0.3, 1.9)	0.8 (-0.3, 2.2)
Estimated glomerular filtration rate	1.0 (-0.1, 2.4)	1.9 (-0.2, 4.2)	0.4 (-0.3, 1.8)	0.3 (-0.6, 1.5)	0.3 (-0.6, 1.4)
All significant physiological factors	6.5 (4.3, 9.7)	7.6 (5.0, 11.7)	NA	6.0 (2.5, 10.9)	6.7 (2.8, 12.5)
Diabetes related status					
Family history of diabetes	0.7 (0.1, 1.6)	0.6 (0.0, 1.5)	0.3 (-0.4, 1.4)	0.0 (-0.7, 0.5)	0.0 (-0.7, 0.4)
HbA1c	2.6 (1.3, 4.4)	3.4 (1.7, 5.8)	1.5 (-0.7, 4.6)	3.7 (1.8, 6.7)	4.0 (1.8, 7.4)
Diabetes duration	0.0 (-1.3, 1.1)	0.0 (-1.3, 1.3)	0.0 (-0.7, 0.7)	2.5 (1.0, 5.0)	2.7 (1.1, 5.6)
Diabetes medication use	2.1 (0.7, 3.8)	3.0 (1.3, 5.3)	1.3 (0.1, 3.7)	4.2 (2.1, 7.7)	4.4 (2.2, 7.9)
All significant diabetes related status	4.6 (2.8, 7.3)	5.6 (3.2, 9.5)	NA	7.2 (4.4, 12.0)	7.7 (4.6, 13.3)
Comorbid conditions					
chronic kidney disease	1.7 (0.3, 3.5)	2.0 (0.2, 4.0)	NA	0.7 (0.0, 2.0)	0.9 (0.0, 2.4)
Diabetes-related microvascular disease	1.4 (0.3, 2.9)	2.3 (0.5, 4.7)	2.2 (0.3, 6.1)	2.3 (0.9, 4.5)	2.1 (0.8, 4.3)
Neurodegenerative disease	1.1 (0.2, 2.3)	0.4 (-0.3, 1.4)	0.3 (-1.1, 2.7)	0.2 (-0.8, 1.3)	0.2 (-0.8, 1.5)
Respiratory disease	3.0 (1.4, 5.0)	2.6 (1.0, 4.8)	1.9 (-0.1, 5.5)	1.5 (0.2, 3.8)	1.4 (-0.2, 3.6)
Digestive disease	1.6 (0.5, 2.9)	1.0 (0.1, 2.3)	0.2 (-1.2, 1.9)	0.4 (0.0, 1.4)	0.5 (-0.1, 1.5)
Rheumatoid arthritis	NA	NA	NA	0.0 (-0.5, 0.6)	0.0 (-0.7, 0.7)
Osteoarthritis	0.2 (-0.3, 0.7)	0.0 (-0.6, 0.8)	0.3 (-0.7, 1.8)	1.1 (0.1, 2.6)	1.2 (0.1, 2.9)
All significant comorbid conditions	8.4 (5.4, 12.4)	7.3 (3.9, 12.0)	NA	4.9 (2.3, 8.4)	4.1 (1.9, 7.7)
All significant mediators[†]	37.6 (28.7, 51.6)	38.0 (28.0, 55.6)	19.8 (10.2, 42.4)	29.8 (20.3, 47.1)	32.3 (20.8, 56.6)

Results marked in BOLD were statistically significant. NA: proportion mediated was not calculated when the point estimate of the direct effect was in a direction opposite to that of the indirect effect.

*Mediation analysis adjusted for age, sex, ethnicity, assessment centre, current employment status, education level, and Townsend Deprivation Index.

†All significant mediators of single mediation analyses are included in the multiple mediation analyses.

CVD, cardiovascular disease; MACE, major adverse cardiovascular events; MET, metabolic equivalent of task.

eTable 20. Hazard ratios and 95% CI from the Fine-Gray subdistribution Hazard Models for composites of incident myocardial infarction or stroke

Variables	Model 1*		Model 2†		Model 3‡	
	sHR (95% CI)	P value	sHR (95% CI)	P value	sHR (95% CI)	P value
Social isolation						
Least isolated	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Moderately isolated	1.07 (0.96-1.20)	0.220	0.98 (0.87-1.10)	0.760	0.97 (0.86-1.09)	0.610
Most isolated	1.21 (1.06-1.39)	0.006	0.98 (0.85-1.13)	0.800	0.97 (0.83-1.12)	0.640
Items of social isolation						
Contact with family/friends/groups						
More	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Little	1.08 (0.98-1.19)	0.140	0.96 (0.87-1.07)	0.500	0.95 (0.86-1.06)	0.350
Live alone						
No	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Yes	1.14 (1.02-1.28)	0.026	1.00 (0.88-1.13)	0.990	0.99 (0.88-1.12)	0.940
Loneliness						
No	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Yes	1.57 (1.33-1.86)	<0.001	1.32 (1.11-1.57)	0.002	1.30 (1.10-1.55)	0.003
Items of loneliness						
Lonely						
No	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Yes	1.38 (1.23-1.55)	<0.001	1.17 (1.04-1.33)	0.011	1.16 (1.02-1.31)	0.020
Able to confide						

Usually	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Never/Almost never	1.28 (1.14-1.44)	<0.001	1.18 (1.04-1.33)	0.009	1.16 (1.03-1.31)	0.014

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation/loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 21. Multivariable-adjusted hazard ratios of mortality and composites of myocardial infarction or stroke for social isolation across subgroups

	All-cause mortality			Composites of incident myocardial infarction or stroke		
	Moderately vs. least	Most vs. least	P _{interaction}	Moderately vs. least	Most vs. least	P _{interaction}
	HR (95% CI)	HR (95% CI)*		HR (95% CI)	HR (95% CI)*	
Age			0.308			0.749
<60	1.10 (0.91-1.33)	1.37 (1.11-1.68)		1.01 (0.84-1.22)	0.97 (0.78-1.20)	
≥60	1.16 (1.06-1.28)	1.30 (1.15-1.47)		1.01 (0.90-1.13)	1.02 (0.89-1.18)	
Sex			0.996			0.635
Female	1.16 (0.99-1.36)	1.22 (1.00-1.49)		1.00 (0.84-1.19)	0.88 (0.70-1.10)	
Male	1.15 (1.04-1.28)	1.36 (1.21-1.55)		1.02 (0.91-1.14)	1.06 (0.92-1.21)	
Ethnicity			0.463			0.037
Non-white	1.14 (1.04-1.25)	1.33 (1.20-1.49)		1.05 (0.95-1.16)	1.06 (0.93-1.20)	
White	1.35 (0.98-1.86)	1.31 (0.89-1.94)		0.78 (0.58-1.03)	0.70 (0.49-1.02)	
Townsend Deprivation Index			0.470			0.709
Tertile 1	0.98 (0.84-1.14)	1.26 (1.03-1.55)		0.99 (0.84-1.17)	1.03 (0.82-1.30)	
Tertile 2	1.21 (1.04-1.41)	1.36 (1.12-1.64)		0.97 (0.83-1.15)	1.11 (0.91-1.37)	
Tertile 3	1.34 (1.15-1.57)	1.48 (1.25-1.76)		1.09 (0.93-1.29)	0.96 (0.79-1.16)	
Smoking status			0.583			0.059
Never	1.24 (1.07-1.43)	1.31 (1.09-1.56)		0.93 (0.80-1.08)	0.87 (0.72-1.05)	
Previous	1.12 (0.99-1.26)	1.29 (1.11-1.51)		1.10 (0.96-1.26)	1.06 (0.88-1.27)	
Current	1.17 (0.92-1.49)	1.48 (1.15-1.92)		1.06 (0.81-1.39)	1.21 (0.90-1.63)	
Alcohol consumption status			0.474			0.438

Not current	1.23 (0.98-1.56)	1.65 (1.28-2.11)		0.97 (0.76-1.24)	0.93 (0.70-1.24)
Less than three times a week	1.20 (1.06-1.36)	1.22 (1.05-1.41)		1.13 (0.99-1.29)	1.12 (0.95-1.31)
Three or more times a week	1.06 (0.91-1.23)	1.40 (1.15-1.69)		0.88 (0.75-1.04)	0.88 (0.70-1.12)
Physical activity (MET Score)			0.081		0.303
Tertile 1	1.19 (1.03-1.36)	1.22 (1.03-1.43)		1.03 (0.88-1.20)	1.00 (0.83-1.20)
Tertile 2	1.01 (0.87-1.18)	1.37 (1.14-1.64)		0.93 (0.79-1.09)	0.98 (0.80-1.21)
Tertile 3	1.30 (1.10-1.54)	1.56 (1.26-1.92)		1.10 (0.92-1.30)	1.03 (0.82-1.31)
Obesity status			0.519		0.436
Underweight or normal weight	1.07 (0.92-1.25)	1.34 (1.11-1.62)		1.00 (0.85-1.17)	1.05 (0.85-1.29)
Overweight	1.41 (1.05-1.91)	1.61 (1.13-2.29)		1.02 (0.71-1.46)	1.24 (0.81-1.90)
Obese	1.18 (1.05-1.32)	1.30 (1.14-1.49)		1.02 (0.90-1.16)	0.97 (0.83-1.13)
HbA1c			0.822		0.238
<53 mmol/mol	1.12 (1.00-1.26)	1.30 (1.13-1.50)		1.04 (0.92-1.19)	1.15 (0.98-1.35)
≥53 mmol/mol	1.23 (1.07-1.41)	1.39 (1.19-1.63)		0.99 (0.86-1.14)	0.88 (0.74-1.05)

*HRs were adjusted for age, sex, ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, social isolation/loneliness, estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 22. Multivariable-adjusted hazard ratios of mortality and composites of myocardial infarction or stroke for loneliness across subgroups

	All-cause mortality		Composites of incident myocardial infarction or stroke	
	Loneliness (yes vs. no)		Loneliness (yes vs. no)	
	HR (95% CI)*	P _{interaction}	HR (95% CI)*	P _{interaction}
Age		0.443		0.244
<60	1.00 (0.79-1.27)		1.46 (1.16-1.83)	
≥60	0.96 (0.82-1.14)		1.27 (1.07-1.52)	
Sex		0.955		0.180
Female	0.96 (0.75-1.24)		1.11 (0.84-1.46)	
Male	1.02 (0.87-1.19)		1.47 (1.26-1.73)	
Ethnicity		0.135		0.117
Non-white	1.03 (0.90-1.19)		1.31 (1.13-1.52)	
White	0.64 (0.36-1.13)		1.91 (1.30-2.82)	
Townsend Deprivation Index		0.243		0.773
Tertile 1	1.35 (1.05-1.75)		1.54 (1.17-2.04)	
Tertile 2	0.79 (0.60-1.04)		1.14 (0.87-1.49)	
Tertile 3	0.97 (0.80-1.18)		1.43 (1.17-1.75)	
Smoking status		0.859		0.229
Never	1.07 (0.84-1.36)		1.33 (1.05-1.68)	
Previous	0.90 (0.74-1.11)		1.26 (1.02-1.56)	
Current	1.04 (0.79-1.36)		1.70 (1.27-2.28)	
Alcohol consumption status		0.754		0.601

Not current	0.89 (0.67-1.19)	1.33 (0.98-1.81)	
Less than three times a week	1.14 (0.95-1.37)	1.30 (1.08-1.57)	
Three or more times a week	0.83 (0.63-1.10)	1.60 (1.22-2.11)	
Physical activity (MET Score)			0.746
Tertile 1	1.07 (0.88-1.28)	1.36 (1.11-1.67)	
Tertile 2	0.87 (0.67-1.13)	1.50 (1.18-1.91)	
Tertile 3	1.01 (0.76-1.35)	1.23 (0.92-1.66)	
Obesity status			0.512
Underweight or normal weight	1.04 (0.80-1.36)	1.32 (1.01-1.72)	
Overweight	0.96 (0.61-1.51)	1.58 (0.93-2.71)	
Obese	0.99 (0.84-1.17)	1.37 (1.15-1.62)	
HbA1c			0.134
<53 mmol/mol	0.94 (0.77-1.13)	1.36 (1.12-1.65)	
≥53 mmol/mol	1.06 (0.87-1.28)	1.36 (1.12-1.66)	0.430

*HRs were adjusted for age, sex, ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, social isolation/loneliness, estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.

eTable 23. Multivariable-adjusted hazard ratios of social isolation and loneliness with subsequent risk for mortality, myocardial infarction, and stroke

Outcomes	Exposures	Model 1*		Model 2†		Model 3‡	
		HR (95% CI)	P _{interaction}	HR (95% CI)	P _{interaction}	HR (95% CI)	P _{interaction}
Mortality							
All-cause mortality	Social isolation	1.29 (1.22-1.36)		1.17 (1.11-1.23)		1.15 (1.09-1.22)	
	Loneliness	1.19 (0.91-1.55)		1.02 (0.78-1.33)		1.01 (0.77-1.32)	
	Social isolation*loneliness	1.01 (0.84-1.21)	0.894	0.98 (0.82-1.18)	0.864	0.99 (0.82-1.19)	0.911
CVD mortality	Social isolation	1.34 (1.25-1.45)		1.19 (1.10-1.29)		1.17 (1.08-1.26)	
	Loneliness	1.19 (0.81-1.75)		1.01 (0.69-1.49)		1.00 (0.68-1.48)	
	Social isolation*loneliness	1.03 (0.80-1.33)	0.815	1.01 (0.78-1.31)	0.938	1.02 (0.79-1.33)	0.859
Overall							
Composites of incident myocardial	Social isolation	1.10 (1.03-1.16)		1.01 (0.95-1.08)		1.01 (0.95-1.07)	
	Loneliness	1.67 (1.30-2.14)		1.48 (1.15-1.90)		1.46 (1.13-1.87)	
	Social isolation*loneliness	0.95 (0.80-1.14)	0.603	0.95 (0.79-1.13)	0.543	0.95 (0.79-1.14)	0.574
Fatal events							
Composites of fatal myocardial	Social isolation	1.57 (1.26-1.94)		1.39 (1.11-1.73)		1.38 (1.10-1.72)	
	Loneliness	1.54 (0.55-4.32)		1.34 (0.48-3.79)		1.30 (0.46-3.65)	
	Social isolation*loneliness	0.96 (0.49-1.89)	0.917	0.96 (0.49-1.89)	0.906	0.99 (0.50-1.94)	0.970
Non-fatal events							
Composites of non-fatal myocardial	Social isolation	1.07 (1.00-1.13)		0.99 (0.93-1.05)		0.98 (0.92-1.05)	

Loneliness	1.67 (1.29-2.16)		1.49 (1.15-1.92)		1.47 (1.13-1.90)	
Social isolation*loneliness	0.95 (0.79-1.15)	0.595	0.94 (0.78-1.14)	0.536	0.94 (0.78-1.14)	0.544

*Model 1 adjusted for age and sex;

†Model 2 additionally adjusted for ethnicity, assessment centre, current employment status, education level, Townsend Deprivation Index, smoking status, alcohol consumption status, physical activity (MET Score), TV watching time, healthy diet score, sleep duration, ever seeking help from physicians due to anxiety or depressive symptoms, obesity status, grip strength, systolic blood pressure, diastolic blood pressure, hyperlipidaemia, and social isolation*loneliness;

‡Model 3 additionally adjusted for estimated glomerular filtration rate, family history of diabetes, HbA1c, diabetes duration, diabetes medication use, chronic kidney disease, diabetes-related microvascular disease, neurodegenerative disease, respiratory disease, digestive disease, rheumatoid arthritis, and osteoarthritis.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent of task.