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Observational and genetic evidence disagree on the association between loneliness and risk of multiple diseases

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Loneliness—the subjective experience of social disconnection—is now widely regarded as a health risk factor. However, whether the associations between loneliness and multiple diseases are consistent with causal effects remains largely unexplored. Here we combined behavioural, genetic and hospitalization data from the UK Biobank to examine the associations of loneliness with a wide range of non-overlapping diseases. During a median 12.2-year follow-up, loneliness was associated with greater risks in 13 of 14 disease categories and 30 of 56 individual diseases considered. Of the 30 diseases significantly associated with loneliness, 26 had genetic data available for Mendelian randomization (MR) analyses. After Benjamini–Hochberg correction and multiple sensitivity analyses within the MR framework, non-causal associations were identified between genetic liability to loneliness and 20 out of the 26 specific diseases, including cardiovascular diseases, type 2 diabetes mellitus, obesity, chronic liver diseases, chronic kidney disease, most neurological diseases and the other common diseases. Genetic liability to loneliness was only potentially causally associated with the remaining six diseases. Socioeconomic factors, health behaviours, baseline depressive symptoms and comorbidities largely explained the associations between loneliness and diseases. Overall, our study revealed a dissociation between observational and genetic evidence regarding the associations of loneliness with multiple diseases. These findings suggest that loneliness may serve as a potential surrogate marker rather than a causal risk factor for most diseases tested here.

Meaningful social connection is pivotal for maintaining both physical and mental health[1,2]. Loneliness is the subjective aspect of social disconnection, distinct from social isolation (objective social disconnection); specifically, it is a painful feeling arising from a mismatch between the desired levels of meaningful social associations and actual levels of social contacts[3]. One can still feel lonely even if one has many interactions with others. Approximately 2.4–24.2% of middle-aged and older adults in Europe perceive feelings of loneliness[4], and this rate has dramatically increased since the coronavirus disease 2019 (COVID-19) pandemic[5].

Theoretical models have suggested that loneliness may initiate complex biological and behavioural mechanisms, such as an excessive stress response[6–8], elevated levels of inflammation[9], or inhibited reward or motivation[8], that weaken overall health and subsequently increase an individual's susceptibility to various diseases[6,10]. As a response, in May 2023, the US Surgeon General stated that the pandemic of loneliness is

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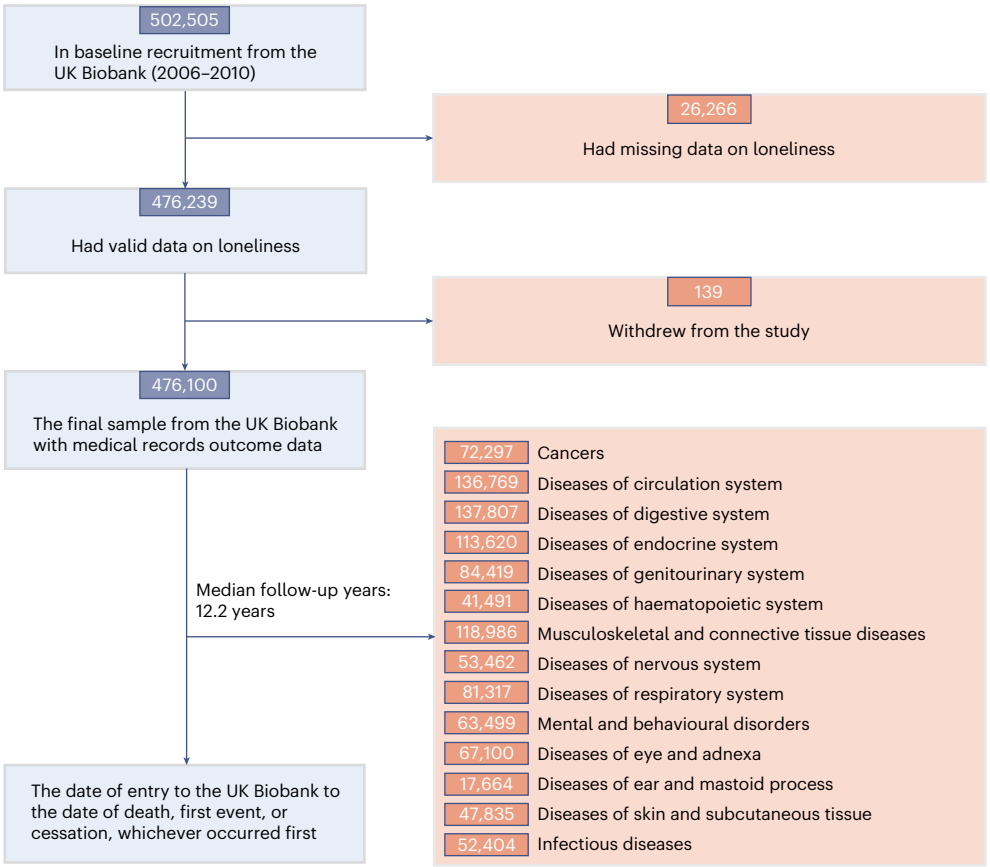

Fig. 1 | Study profile. The study included 476,100 participants with valid and complete answers about loneliness. We excluded participants with a diagnosis of each disease at baseline, respectively.

threatening public health[11]. However, the associations between loneliness and a wide range of common diseases are poorly understood. Our recent findings[12–16] and previous observational evidence[17–21] have indicated that loneliness is associated with increased risks of several physical and mental diseases and premature death. However, most of these studies focus narrowly on single disease. To our knowledge, the associations of loneliness with other major diseases, such as chronic kidney disease and sleep apnoea, have not been studied. Moreover, the most frequent causes of hospitalization among individuals experiencing loneliness also remain uncertain. Importantly, outcome-wide investigations would facilitate direct comparisons of associations with different diseases and identification of null findings by avoiding investigator bias[22]. However, we are not aware of outcome-wide studies concerning loneliness.

Another important question is whether loneliness causally influences the risk for multiple diseases or whether these associations can be explained by reverse causation. Observational evidence suggests that individuals with poorer physical and mental health tend to have a greater rate of loneliness[3,5]. However, few studies have simultaneously investigated bidirectional causal associations between loneliness and a wide range of diseases. Despite epidemiological studies yielding robust associations, reverse causation and residual confounding are inevitable due to the observational nature of these studies[23]. Compared with observational studies, Mendelian randomization (MR) studies leverage genetic variants as proxies for life-long exposure risks and can suggest a potential causal association[24]. Several pioneering MR studies have revealed potentially causal associations between loneliness and depression[25] or diabetes[20]; conversely, another MR study reported non-causal associations between loneliness and some cardiovascular traits[26]. However, such causal evidence for other common diseases is still limited. In addition, once disease-specific associations have been established, explanatory factors that differentially associate loneliness with the risks of different diseases can be explored.

To fill these gaps, capitalizing on a large sample of individuals with behavioural, genetic and hospitalization data from the UK Biobank, the primary aim of the present study was to establish the associations between loneliness and the incidence of 56 individual diseases across 14 disease categories. The secondary aim was to identify any potentially causal associations between loneliness and identified disease outcomes in the UK Biobank study using MR. In addition, we investigated the factors explaining the associations between loneliness and each disease identified.

Results

Baseline characteristics

In the current study sample from the UK Biobank (Fig. 1), the mean age was 56.5 years, 259,806 (54.6%) out of 476,100 participants were women, and 23,136 (4.9%) were categorized as having loneliness (Table 1). Compared with participants without loneliness, those with loneliness were generally more likely to be female and obese, have lower education levels and more frequently engage in unhealthy habits, including smoking and physical inactivity. The baseline characteristics of the population from the two supporting cohorts, the China Health and Retirement Longitudinal Study (CHARLS) and the Health and Retirement Study (HRS), are shown in Supplementary Tables 1 and 2.

Associations between loneliness and incident diseases

Figure 2 shows the associations of loneliness with the incidence of various disease categories and individual diseases among the UK Biobank participants. After a median follow-up of 12.2 [interquartile range

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Table 1 | Baseline characteristics of participants in the UK Biobank by loneliness status

Characteristics	Total (*N*=476,100)	No loneliness (*N*=452,964)	Loneliness (*N*=23,136)
Age (years) (mean (s.d.))	56.5 (8.1)	56.6 (8.1)	56.0 (8.0)
Sex, female, *n* (%)	259,806 (54.6)	204,492 (45.1)	11,802 (51.0)
Ethnicity, White, *n* (%)	453,466 (95.2)	431,764 (95.3)	21,702 (93.8)
Assessment centre, *n* (%)			
England	422,064 (88.7)	401,733 (88.7)	20,331 (87.9)
Scotland	34,203 (7.2)	32,451 (7.2)	1,752 (7.6)
Wales	19,833 (4.2)	18,780 (4.1)	1,053 (4.6)
College or university degree, *n* (%)	157,129 (33.0)	151,691 (33.5)	5,438 (23.5)
Currently employed, *n* (%)	277,130 (58.2)	264,824 (58.5)	12,306 (53.2)
Smoking status, *n* (%)			
Never	260,119 (54.6)	249,075 (55.0)	11,044 (47.7)
Previous	165,834 (34.8)	157,968 (34.9)	7,866 (34.0)
Current	50,147 (10.5)	45,921 (10.1)	4,226 (18.3)
Alcohol intake frequency, *n* (%)			
Not current	36,806 (7.7)	34,127 (7.5)	2,679 (11.6)
Two or less times a week	230,713 (48.5)	218,341 (48.2)	12,372 (53.5)
Three or more times a week	208,581 (43.8)	200,496 (44.3)	8,085 (34.9)
BMI ($kg\,m^{-2}$) (mean (s.d.))	27.4 (4.8)	27.4 (4.8)	28.5 (5.5)
Physical activity (min/week) (mean (s.d.))	402.3 (512.9)	402.9 (510.9)	390.2 (551.5)

(IQR), 10.6–13.8] years, loneliness was associated with a greater risk for 13 out of 14 disease categories [adjusted hazard ratio (aHR) range, 1.14–1.61; population-attributable fraction (PAF) range, 0.66%–2.76%] after adjusting for age, sex, ethnicity, education level, employment, smoking status, alcohol intake frequency, body mass index (BMI) and physical activity. These associations remained significant even after accounting for multiple comparisons using Bonferroni correction. Compared with individuals who did not experience loneliness, those who experienced loneliness had the greatest risk of developing mental and behavioural disorders (aHR, 1.61; 95% confidence interval (CI), 1.57–1.66; PAF, 2.76%), followed by the risk of infectious diseases and diseases of the nervous system, respiratory system, endocrine system, haematopoietic system, ear and mastoid process, musculoskeletal and connective tissue, circulation system, digestive system, eye and adnexa, genitourinary system and skin and subcutaneous tissue (aHR range, 1.14–1.30; PAF range, 0.66–1.42%).

As shown in Fig. 2, in terms of individual diseases, after correcting for possible confounders and multiple comparisons, loneliness was associated with an increased subsequent risk for 30 out of 56 individual diseases (aHR range, 1.18–2.18; PAF range, 0.86%–5.42%). Posttraumatic stress disorder (aHR, 2.18; 95% CI, 1.68–2.85; PAF, 5.42%), depression (aHR, 2.15; 95% CI, 2.06–2.24; PAF, 5.18%), anxiety (aHR, 1.82; 95% CI, 1.74–1.91; PAF, 3.81%), schizophrenia (aHR, 1.81; 95% CI, 1.43–2.30; PAF, 3.78%) and chronic obstructive pulmonary disease (aHR, 1.51; 95% CI, 1.44–1.59; PAF, 2.40%) were the five diseases most strongly associated with loneliness among the UK Biobank participants. The associations between the two items of loneliness ('feeling lonely' and 'able to confide') and the incidence of individual diseases and disease categories were generally consistent with the associations observed for loneliness (Supplementary Table 3). The overall pattern of loneliness–disease associations in the UK Biobank dataset was largely consistent with that observed in the CHARLS and HRS datasets. Across these two supporting cohorts, loneliness had the strongest association with mental and behavioural disorders, followed by associations with diseases of the respiratory, digestive, nervous and circulatory systems (CHARLS: aHR range, 1.16–2.10; HRS: aHR range, 1.16–1.65) (Supplementary Tables 4 and 5).

Negative control, sensitivity and subgroup analyses

The negative control analyses of the exposure data did not show the same pattern as the main analyses (Supplementary Tables 6 and 7). The analyses using the 'frequency of travelling from home to job workplace' as a negative control exposure showed no statistically significant associations with the risks for most of the diseases of interest. The 'frequency of travelling from home to job workplace' had modest associations with several mental disorders; however, the effect sizes were substantially smaller than those for loneliness (Supplementary Table 6). Similarly, when 'usual side of head for mobile phone use' was treated as an alternative negative control exposure, we found no statistically significant associations between loneliness and any disease outcome of interest, except for modest associations with chronic obstructive pulmonary disease and hearing loss (Supplementary Table 7). On the negative control outcome side, we observed no statistically significant association between loneliness and the risk of injury in transport accidents (aHR, 1.09, 95% CI, 0.84–1.41) (Supplementary Table 8).

The major results were generally robust across the following sensitivity analyses, including repeating the analyses by excluding participants with any missing covariate data (Supplementary Table 9), excluding events occurring within the first 2 years (Supplementary Table 10), calculating Fine–Gray subdistribution hazards (Supplementary Table 11) and further adjusting for social isolation (Supplementary Table 12). In addition, the results were largely similar in a subsample restricted to participants without long-standing illness, disability or infirmity at baseline (Supplementary Table 13) or participants without self-reported depressive symptoms at baseline (Supplementary Table 14). Associations between loneliness and incident diseases were generally consistent across subgroups stratified by age (<60 years or ≥60 years), sex (male or female) and obesity status (underweight or normal, overweight or obese) (Supplementary Tables 15–17).

Disease burden among individuals experiencing loneliness

To describe the disease burden of loneliness, we computed the 10-year cumulative incidence rate (CIR) for the 14 disease categories among individuals in the UK Biobank experiencing loneliness (Fig. 3). The highest CIR was observed for diseases of the digestive (CIR, 360 per 1,000 persons) and circulatory (CIR, 335 per 1,000 persons) systems, followed by musculoskeletal and connective tissue diseases (CIR, 281 per 1,000 persons) and diseases of the endocrine system (CIR, 260 per 1,000 persons). The other disease categories had a low CIR (<200 per 1,000 persons). The greatest difference in the CIR between individuals with and without loneliness was observed for mental and behavioural disorders, with 191 per 1,000 persons experiencing loneliness having mental and behavioural disorders, and 99 per 1,000 persons experiencing no loneliness having mental and behavioural disorders (absolute excess risk, 9.19%).

Causal links of genetic liability to loneliness and diseases

Following Benjamini–Hochberg correction, there is little genetic evidence in the meta-analyses conducted on all sources of MR results supporting causal associations between genetic liability to loneliness and 20 out of the 26 individual diseases screened with available genetic sources (Fig. 4a). These 20 diseases included ischaemic heart disease,

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	HR (95% CI)	PAF (95% CI)
Cancers	0.98 (0.94–1.01)	−0.10 (−0.29–0.05)
Liver cancer	1.36 (1.08–1.72)	1.72 (0.39–3.38)
Lung cancer	1.13 (1.02–1.26)	0.63 (0.10–1.25)
Thyroid cancer	0.79 (0.51–1.22)	−1.03 (−2.44–1.06)
Stomach cancer	1.04 (0.81–1.32)	0.19 (−0.93–1.53)
Breast cancer	0.96 (0.87–1.05)	−0.20 (−0.64–0.24)
Bladder cancer	1.05 (0.90–1.23)	0.24 (−0.49–1.11)
Brain cancer	1.16 (0.88–1.52)	0.77 (−0.59–2.46)
Colorectal cancer	1.01 (0.91–1.13)	0.05 (−0.44–0.63)
Kidney cancer	1.15 (0.96–1.38)	0.72 (−0.19–1.81)
Non-Hodgkin lymphoma	1.00 (0.84–1.19)	0.00 (−0.78–0.91)
Oesophagus cancer	1.18 (0.96–1.45)	0.87 (−0.19–2.14)
Prostate cancer	1.04 (0.96–1.13)	0.19 (−0.20–0.63)
Diseases of circulation system	1.18 (1.16–1.21)	0.81 (0.72–0.95)
Ischaemic heart disease	1.29 (1.24–1.34)	1.35 (1.12–1.58)
Stroke	1.25 (1.16–1.36)	1.20 (0.77–1.71)
Atrial fibrillation	1.21 (1.15–1.28)	1.01 (0.72–1.34)
Peripheral arterial disease	1.45 (1.33–1.59)	2.13 (1.57–2.78)
Hypertension	1.20 (1.17–1.23)	0.93 (0.79–1.06)
Diseases of digestive system	1.18 (1.15–1.21)	0.80 (0.67–0.94)
Chronic liver disease	1.35 (1.26–1.44)	1.67 (1.24–2.08)
Gallbladder, biliary tract and pancreas disease	1.22 (1.17–1.26)	1.04 (0.80–1.22)
Inflammatory bowel disease	1.04 (0.90–1.20)	0.19 (−0.49–0.96)
Diseases of endocrine system	1.23 (1.20–1.26)	1.05 (0.92–1.19)
Type 2 diabetes mellitus	1.33 (1.27–1.39)	1.55 (1.27–1.83)
Hyperthyroidism	1.26 (1.08–1.46)	1.25 (0.39–2.19)
Hypothyroidism	1.18 (1.12–1.25)	0.86 (0.58–1.19)
Obesity	1.24 (1.18–1.29)	1.14 (0.86–1.38)
Diseases of genitourinary system	1.16 (1.13–1.20)	0.75 (0.61–0.93)
Chronic kidney disease	1.26 (1.20–1.32)	1.24 (0.96–1.52)
Urolithiasis	1.11 (1.00–1.23)	0.53 (0.00–1.10)
Diseases of haematopoietic system	1.23 (1.18–1.28)	1.09 (0.86–1.33)
Anaemias	1.26 (1.21–1.32)	1.24 (1.00–1.52)
Haematopoietic disease	1.08 (0.96–1.22)	0.39 (−0.19–1.06)
Musculoskeletal and connective tissue diseases	1.20 (1.17–1.23)	0.91 (0.78–1.05)
Gout	1.13 (1.03–1.23)	0.63 (0.15–1.10)
Rheumatoid arthritis	1.22 (1.11–1.34)	1.06 (0.53–1.62)
Systemic lupus erythematosus	1.25 (0.88–1.78)	1.20 (−0.59–3.65)
Diseases of nervous system	1.28 (1.24–1.33)	1.31 (1.12–1.54)
Alzheimer's disease	1.12 (0.95–1.32)	0.58 (−0.24–1.53)
Parkinson's disease	1.20 (1.03–1.40)	0.96 (0.15–1.91)
Epilepsy	1.33 (1.18–1.50)	1.57 (0.86–2.36)
Migraine	1.31 (1.18–1.47)	1.48 (0.87–2.23)
Multiple sclerosis	1.09 (0.83–1.43)	0.44 (−0.83–2.05)
Diseases of respiratory system	1.28 (1.24–1.31)	1.29 (1.11–1.43)
Asthma	1.27 (1.21–1.33)	1.27 (0.99–1.55)
Chronic obstructive pulmonary disease	1.51 (1.44–1.59)	2.40 (2.08–2.76)
Mental and behavioural disorders	1.61 (1.57–1.66)	2.76 (2.58–2.98)
Depression	2.15 (2.06–2.24)	5.18 (4.80–5.56)
Anxiety	1.82 (1.74–1.91)	3.81 (3.46–4.22)
Schizophrenia	1.81 (1.43–2.30)	3.78 (2.04–5.93)
Bipolar affective disorder	1.42 (1.15–1.74)	2.00 (0.72–3.47)
Posttraumatic stress disorder	2.18 (1.68–2.85)	5.42 (3.20–8.25)
Insomnias	1.44 (1.03–2.00)	2.09 (0.15–4.63)
Sleep apnoea	1.35 (1.25–1.47)	1.67 (1.20–2.22)
Psychoactive substance abuse	1.43 (1.37–1.49)	2.01 (1.73–2.28)
Diseases of eye and adnexa	1.18 (1.14–1.22)	0.86 (0.67–1.05)
Glaucoma	1.18 (1.09–1.28)	0.87 (0.44–1.34)
Cataract	1.18 (1.13–1.23)	0.86 (0.63–1.10)
Diseases of ear and mastoid process	1.22 (1.14–1.30)	1.05 (0.67–1.43)
Hearing loss	1.28 (1.18–1.38)	1.34 (0.87–1.81)
Disorders of vestibular function	1.15 (0.97–1.36)	0.72 (−0.15–1.72)
Diseases of skin and subcutaneous tissue	1.14 (1.09–1.18)	0.66 (0.43–0.85)
Atopic dermatitis	0.71 (0.31–1.61)	−1.43 (−3.47–2.88)
Psoriasis	1.30 (1.15–1.47)	1.43 (0.72–2.23)
Infectious diseases	1.30 (1.25–1.34)	1.42 (1.18–1.60)
Gastrointestinal infection	1.36 (1.29–1.44)	1.71 (1.39–2.09)
Influenza	1.18 (0.97–1.43)	0.87 (−0.15–2.05)
Pneumonia	1.34 (1.28–1.41)	1.62 (1.34–1.94)
Urinary tract infection	1.26 (1.19–1.33)	1.24 (0.91–1.57)

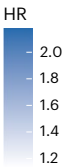

Fig. 2 | Associations of loneliness with diseases among participants from the UK Biobank. aHR was adjusted for age, sex, ethnicity, assessment centre, education level, current employment status, smoking status, alcohol intake frequency, BMI and physical activity.

stroke, atrial fibrillation, peripheral arterial disease, hypertension, chronic liver disease, type 2 diabetes mellitus, obesity, chronic kidney disease, anaemias, rheumatoid arthritis, epilepsy, migraine, chronic obstructive pulmonary disease, anxiety, schizophrenia, glaucoma, cataract, psoriasis and pneumonia. Conversely, genetic liability to loneliness was found to be potentially causally associated with the remaining six specific diseases, namely, hypothyroidism (odds ratio (OR), 2.48; 95% CI, 1.73–3.56), asthma (OR, 2.48; 95% CI, 1.74–3.54), depression (OR, 5.55; 95% CI, 3.67–8.39), sleep apnoea (OR, 2.42; 95% CI, 1.56–3.77), psychoactive substance abuse (OR, 4.46; 95% CI, 2.55–7.77) and hearing loss (OR, 2.04; 95% CI, 1.59–2.61) (Fig. 4a). In the other MR direction (Fig. 4b), after Benjamini–Hochberg correction, we found no potentially bidirectional causal associations from any individual disease to loneliness (Fig. 4b).

We conducted negative control analyses to rule out potential false positive results of our main MR findings in the one-sample MR setting. Regarding negative control exposure, compared with those scoring 1 or 2 for loneliness (N = 106,986), the HRs for most of the disease outcomes

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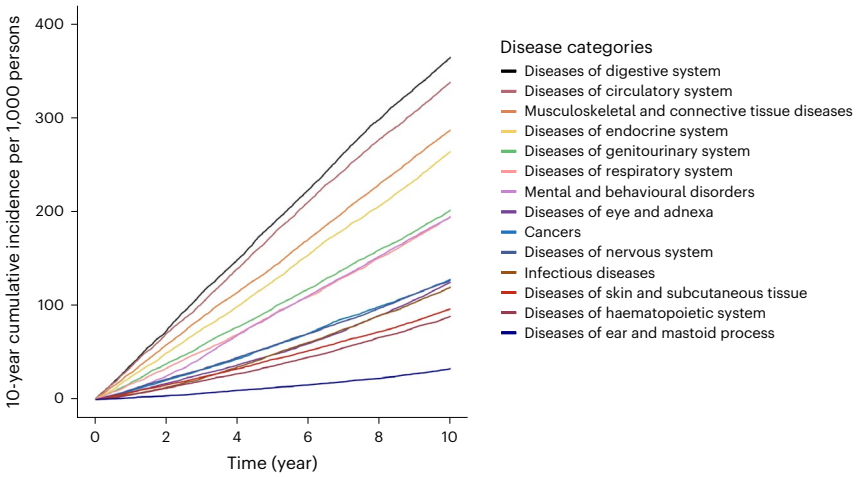

No. risk

Diseases of digestive system	16,823	15,559	14,211	12,867	11,530	10,359
Diseases of circulatory system	18,187	16,884	15,574	14,223	12,959	11,821
Musculoskeletal and connective tissue diseases	18,821	17,630	16,460	15,265	14,031	12,830
Diseases of endocrine system	20,417	19,336	18,224	16,972	15,796	14,521
Diseases of genitourinary system	18,887	18,090	17,226	16,307	15,384	14,442
Diseases of respiratory system	20,595	19,846	18,994	18,053	17,103	16,095
Mental and behavioural disorders	21,673	21,039	19,952	18,873	17,812	16,731
Diseases of eye and adnexa	21,941	21,441	20,799	20,045	19,130	18,071
Cancers	21,680	21,159	20,559	19,824	19,053	18,250
Diseases of nervous system	21,410	20,838	20,181	19,425	18,643	17,767
Infectious diseases	22,112	21,721	21,087	20,321	19,517	18,648
Diseases of skin and subcutaneous tissue	21,452	21,001	20,444	19,803	19,141	18,365
Diseases of haematopoietic system	22,330	21,949	21,437	20,798	20,086	19,314
Diseases of ear and mastoid process	22,757	22,525	22,148	21,704	21,206	20,567
	0	2	4	6	8	10

Time (year)

Fig. 3 | Disease burden among individuals experiencing loneliness from the UK Biobank. The disease burden was measured by 10-year cumulative incidence rate for the 14 disease categories.

were significantly lower among individuals who scored 0 for loneliness (Supplementary Table 18). Regarding negative control outcome, no statistically significant association between genetic liability to loneliness and the negative control outcome 'injury in transport accident' was observed (Supplementary Table 19).

The main results were largely consistent with those from the MR sensitivity analyses. We detected heterogeneity in the analyses of most outcomes across single nucleotide polymorphisms (SNPs) in both directions, indicating that different SNPs had inconsistent effects on the outcomes (Supplementary Tables 20 and 21). To detect and address horizontal pleiotropy, we utilized the MR-Egger intercept analyses, the MR pleiotropy Residual Sum and Outlier (MR-PRESSO), and the Latent Heritable Confounder MR (LHC-MR) analyses. MR-Egger intercept analyses did not find any potential horizontal pleiotropy in both directions (Supplementary Tables 20 and 21). In the MR-PRESSO analyses for both directions, one to three outliers were identified. After removing these outliers, the associations for most diseases remained robust in both directions (Supplementary Tables 20 and 21). In the LHC-MR analyses, the results were largely consistent with those of the main analyses. Despite observing potential effects of genetic confounders on hypothyroidism from EBI and on depression and hearing loss from FinnGen, the effect sizes of these genetic confounders were relatively small (0.075 for hypothyroidism, 0.138 for depression, 0.105 for hearing loss) (Supplementary Tables 20 and 21). In addition, we found that the potentially causal associations from loneliness to disease outcomes remained robust in the sensitivity analyses by excluding SNPs related to depression (Supplementary Table 22) and using multivariable MR analyses accounting for genetic liability to depression (Supplementary Table 23) and BMI (Supplementary Table 24). The mtCOJO analysis results also remained generally consistent with the main results (Supplementary Table 25).

The transcriptome-wide association studies (TWAS) revealed that predicted gene expression related to loneliness was significantly associated with the following cells, tissues or organs: the amygdala, basal ganglia, cerebellum, visceral adipose tissue, thyroid, gastroesophageal junction, transverse colon, cultured fibroblasts and mammary tissue (Supplementary Fig. 1).

Explanatory factors linking loneliness to multiple diseases

As shown in Fig. 5 and Supplementary Fig. 2, the associations between loneliness and various diseases were largely or even completely explained by other factors. Baseline depressive symptoms seemed to explain the largest proportion of the associations between loneliness and diseases (percentage of excess risk mediated (PERM) range, 49%–87%), especially for mental and behaviour disorders (PERM range, 61%–87%). In contrast, socioeconomic factors (PERM range, 15%–41%), health behaviours (PERM range, 5%–47%) and comorbidities (PERM range, 26%–53%) mainly explained the associations between loneliness and physical diseases. Metabolic factors were stronger explanatory factors for diseases of the endocrine system (PERM range, 27%–57%) than for other diseases. Inflammatory factors were also potential explanatory factors for loneliness–disease associations, with the PERM range of 2%–18%.

Discussion

The present study offers a comprehensive examination of the potential associations of loneliness with a wide range of non-overlapping diseases across multiple disease categories (30 out of 56 individual

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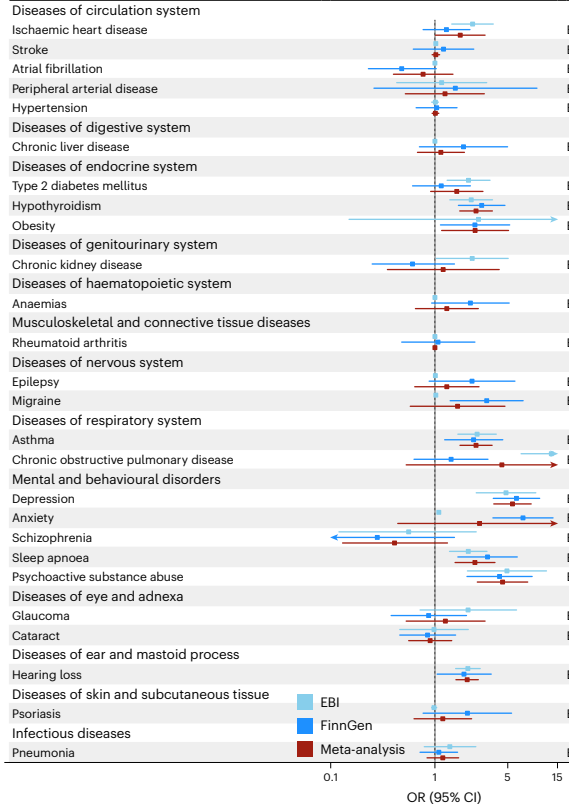
Outcomes	SNP numbers	Cases/controls	OR (95% CI)	Meta-analysis *P* value	Adjusted *P* value	I^2 %
Diseases of circulation system						
Ischaemic heart disease	EBI: 75; FinnGen: 76	91,271/547,753	1.75 (1.01–3.03)	0.047*	0.153	62.7
Stroke	EBI: 80; FinnGen: 76	129,551/1,402,529	1.02 (0.94–1.11)	0.583	0.735	0
Atrial fibrillation	EBI: 80; FinnGen: 77	48,998/615,944	0.77 (0.40–1.49)	0.442	0.722	72.8
Peripheral arterial disease	EBI: 78; FinnGen: 79	9,057/793,863	1.25 (0.52–2.98)	0.622	0.735	0
Hypertension	EBI: 74; FinnGen: 74	228,592/598,445	1.01 (0.94–1.09)	0.776	0.807	0
Diseases of digestive system						
Chronic liver disease	EBI: 81; FinnGen: 79	23,043/804,054	1.14 (0.68–1.92)	0.618	0.735	38
Diseases of endocrine system						
Type 2 diabetes mellitus	EBI: 78; FinnGen: 78	87,955/734,455	1.62 (0.91–2.89)	0.103	0.298	54.6
Hypothyroidism	EBI: 74; FinnGen: 76	87,515/694,309	2.48 (1.73–3.56)	<0.001*	<0.001*	0
Obesity	EBI: 81; FinnGen: 76	18,911/779,837	2.43 (1.16–5.09)	0.018*	0.067	0
Diseases of genitourinary system						
Chronic kidney disease	EBI: 80; FinnGen: 78	16,203/804,871	1.20 (0.35–4.14)	0.768	0.807	78.2
Diseases of haematopoietic system						
Anaemias	EBI: 81; FinnGen: 76	29,089/561,262	1.30 (0.65–2.61)	0.464	0.722	68.9
Musculoskeletal and connective tissue diseases						
Rheumatoid arthritis	EBI: 81; FinnGen: 77	16,605/700,494	1.00 (0.98–1.02)	0.997	0.997	0
Diseases of nervous system						
Epilepsy	EBI: 81; FinnGen: 78	14,254/745,360	1.30 (0.64–2.65)	0.472	0.722	64.3
Migraine	EBI: 81; FinnGen: 78	29,876/735,289	1.65 (0.58–4.70)	0.349	0.648	86.6
Diseases of respiratory system						
Asthma	EBI: 80; FinnGen: 78	86,476/539,367	2.48 (1.74–3.54)	<0.001*	<0.001*	0
Chronic obstructive pulmonary disease	EBI: 77; FinnGen: 78	33,957/901,187	4.39 (0.53–36.49)	0.171	0.404	94.1
Mental and behavioural disorders						
Depression	EBI: 80; FinnGen: 75	91,977/329,410	5.55 (3.67–8.39)	<0.001*	<0.001*	0
Anxiety	EBI: 80; FinnGen: 78	43,125/788,426	2.68 (0.44–16.10)	0.282	0.611	96.7
Schizophrenia	EBI: 79; FinnGen: 78	12,614/775,252	0.41 (0.13–1.32)	0.136	0.354	0
Sleep apnoea	EBI: 64; FinnGen: 79	60,449/644,688	2.42 (1.56–3.77)	<0.001*	<0.001*	13.6
Psychoactive substance abuse	EBI: 81; FinnGen: 77	29,835/392,224	4.46 (2.55–7.77)	<0.001*	<0.001*	0
Diseases of eye and adnexa						
Glaucoma	EBI: 79; FinnGen: 79	22,433/468,045	1.26 (0.53–3.03)	0.599	0.735	37.3
Cataract	EBI: 81; FinnGen: 78	65,828/728,811	0.90 (0.56–1.45)	0.666	0.753	0
Diseases of ear and mastoid process						
Hearing loss	EBI: 75; FinnGen: 78	142,628/626,199	2.04 (1.59–2.61)	<0.001*	<0.001*	0
Diseases of skin and subcutaneous tissue						
Psoriasis	EBI: 79; FinnGen: 76	10,834/655,049	1.19 (0.63–2.25)	0.583	0.735	54.2
Infectious diseases						
Pneumonia	EBI: 79; FinnGen: 78	68,908/753,890	1.19 (0.84–1.69)	0.335	0.648	0



b

Exposures	SNP numbers	Cases/controls	OR (95% CI)	Meta-analysis *P* value	Adjusted *P* value	I^2 %
Diseases of circulation system						
Ischaemic heart disease	EBI: 366; FinnGen: 183	91,271/547,753	1.0037(0.9987–1.0087)	0.152	0.359	85.2
Stroke	EBI: 13; FinnGen: 46	129,551/1,402,529	1.0036(0.9579–1.0514)	0.884	0.953	0
Atrial fibrillation	EBI: 38; FinnGen: 223	48,998/615,944	1.0003(0.9941–1.0066)	0.916	0.953	0
Peripheral vascular disease	EBI: 29; FinnGen: 9	9,057/793,863	0.9994(0.9977–1.0012)	0.518	0.641	0
Hypertension	EBI: 642; FinnGen:485	228,592/598,445	1.0058(0.9964–1.0153)	0.226	0.452	56.8
Diseases of digestive system						
Chronic liver disease	EBI: 37; FinnGen: 13	23,043/804,054	0.9998(0.9693–1.0312)	0.988	0.988	0
Diseases of endocrine system						
Type 2 diabetes mellitus	EBI: 407; FinnGen: 416	87,955/734,455	1.0019(1.0003–1.0034)	0.018*	0.124	0
Hypothyroidism	EBI: 307; FinnGen: 308	87,515/694,309	1.0011(0.9987–1.0035)	0.385	0.604	71.2
Obesity	EBI: 6; FinnGen: 116	18,911/779,837	1.0035(1.0004–1.0065)	0.026*	0.134	69
Diseases of genitourinary system						
Chronic kidney disease	EBI: 12; FinnGen: 17	16,203/804,871	0.9966(0.9929–1.0002)	0.062	0.202	0
Diseases of haematopoietic system						
Anaemias	EBI: 19; FinnGen: 21	29,089/561,262	1.0110(0.9408–1.0865)	0.765	0.865	0
Musculoskeletal and connective tissue diseases						
Rheumatoid arthritis	EBI: 37; FinnGen: 81	16,605/700,494	1.1325(0.8687–1.4765)	0.358	0.604	88.9
Diseases of nervous system						
Epilepsy	EBI: 16; FinnGen: 15	14,254/745,360	1.1217(0.8195–1.5354)	0.473	0.641	67.6
Migraine	EBI: 54; FinnGen: 27	29,876/735,289	1.0686(0.9169–1.2454)	0.396	0.604	81.3
Diseases of respiratory system						
Asthma	EBI: 173; FinnGen: 122	86,476/539,367	1.0029(1.0005–1.0052)	0.016*	0.124	0
Chronic obstructive pulmonary disease	EBI: 44; FinnGen: 61	33,957/901,187	1.0029(0.9987–1.0071)	0.175	0.379	35
Mental and behavioural disorders						
Depression	EBI: 16; FinnGen: 72	91,977/329,410	1.0133(1.0021–1.0246)	0.019*	0.124	80
Anxiety	EBI: 19; FinnGen: 41	43,125/788,426	1.1746(0.8547–1.6144)	0.321	0.596	88.4
Schizophrenia	EBI: 13; FinnGen: 19	12,614/775,252	1.0009(0.9983–1.0035)	0.498	0.641	0
Sleep apnoea	EBI: 46; FinnGen: 84	60,449/644,688	1.0073(0.9975–1.0171)	0.144	0.359	68.5
Psychoactive substance abuse	EBI: 10; FinnGen: 75	29,835/392,224	1.0047(1.0013–1.0081)	0.007*	0.124	0
Diseases of eye and adnexa						
Glaucoma	EBI: 50; FinnGen: 118	22,433/468,045	0.9986(0.9967–1.0004)	0.126	0.359	0
Cataract	EBI: 34; FinnGen: 83	65,828/728,811	1.0035(1.0003–1.0067)	0.031*	0.134	0
Diseases of ear and mastoid process						
Hearing loss	EBI: 107; FinnGen: 64	142,628/626,199	1.0048(1.0001–1.0096)	0.048*	0.178	35
Diseases of skin and subcutaneous tissue						
Psoriasis	EBI: 42; FinnGen: 81	10,834/655,049	1.0096(0.9865–1.0332)	0.418	0.604	64.3
Infectious diseases						
Pneumonia	EBI: 6 ; FinnGen: 27	68,908/753,890	1.0012(0.9967–1.0057)	0.603	0.713	0

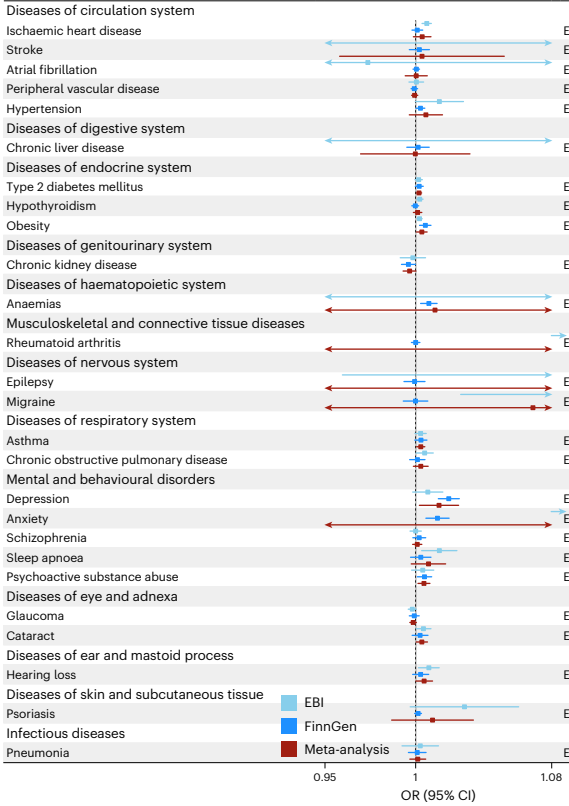


Fig. 4 | Causal associations between loneliness and 26 diseases using the MRE-IVW method. a, Causal effects of loneliness on diseases. **b**, Causal effects of diseases on loneliness. Adjusted *P* value refers to the *P* value after Benjamini–Hochberg correction. I^2 values <25%, 25–75% and >75% were considered to indicate low, moderate and high heterogeneity, respectively. *$P < 0.05$.

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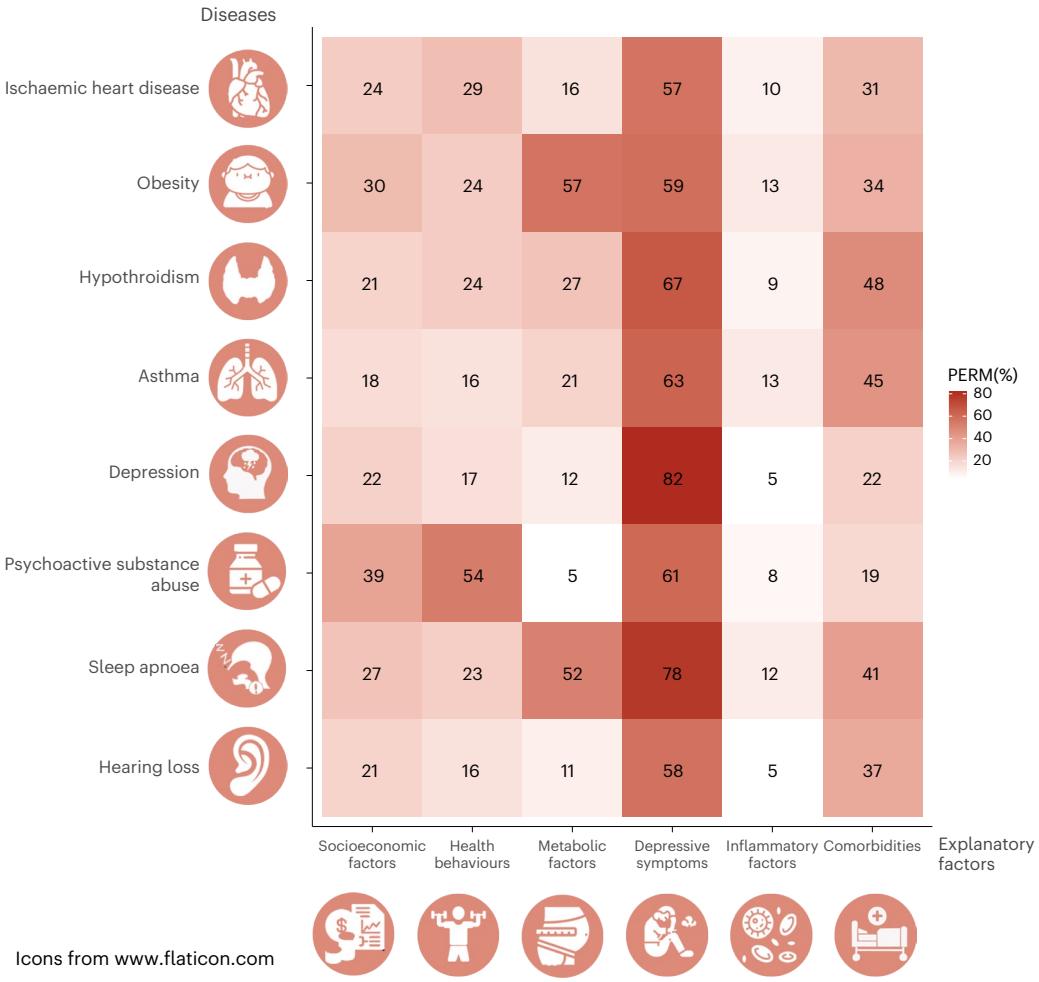

Fig. 5 | Proportions of associations between loneliness and nine diseases attributable to different explanatory factors. Minimally adjusted for age, sex, ethnicity and assessment centre. (1) Socioeconomic factors: education level, Townsend Deprivation Index and employment; (2) health behaviours: health diet score, smoking status, alcohol intake frequency, sleep duration and physical activity; (3) metabolic factors: BMI, SBP, DBP, glucose and LDL-C; (4) depressive symptoms; depression scores measured by PHQ-2; (5) inflammatory factors: leucocytes, platelets, platelet crit, lymphocytes, monocytes, neutrophils, eosinophils, basophils, C-reactive protein; and (6) comorbidities: history of long-standing illness, use of diabetes medication, use of cholesterol-lowering medication and use of antihypertensive medication. Fully adjusted for age, sex, ethnicity, assessment centre, Townsend Deprivation Index, education level, current employment status, healthy diet score, smoking status, alcohol intake frequency, BMI, sleep duration, physical activity, SBP, DBP, glucose, LDL-C, leucocytes, platelets, platelet crit, lymphocytes, monocytes, neutrophils, eosinophils, basophils, C-reactive protein, depression symptoms, history of long-standing illness, use of diabetes medication, use of cholesterol-lowering medication and use of antihypertensive medication.

diseases and 13 out of 14 disease categories considered) using data from the UK Biobank. Most of these associations from observational analyses were consistent with those identified in two other racially diverse cohorts, the CHARLS and HRS cohorts. The greatest health risk attributable to loneliness was the risk of mental and behavioural disorders, followed by the risk of infectious diseases, and diseases of the nervous, respiratory and endocrine systems. However, our MR analyses provided little causal evidence for the associations between loneliness and most specific diseases that were identified in the observational analyses, such as associations with cardiovascular diseases, type 2 diabetes mellitus, obesity, chronic liver diseases, chronic kidney diseases and most neurological diseases. Potentially causal associations were only found between loneliness and only 6 out of 26 diseases, including hypothyroidism, asthma, depression, psychoactive substance abuse, sleep apnoea and hearing loss. Ultimately, socioeconomic factors, health behaviours, metabolic factors, baseline depressive symptoms, inflammatory factors and comorbidities explained more than 79% of the associations between loneliness and disease. Overall, our investigation of a range of outcomes advanced the literature by providing new evidence supporting a dissociation between observational and genetic evidence regarding the associations of loneliness with most tested diseases. Thus, loneliness may serve as a potential surrogate marker instead of a causal risk factor for most diseases tested.

Building on existing studies that mostly focused on single outcomes[12,14–21], we showed that loneliness is prospectively associated with a greater risk of developing a wide range of adverse health outcomes, including 30 diseases across 13 disease categories. Notably, we discovered approximately 20 additional diseases associated with loneliness that are yet to be studied in the general population, such as chronic kidney disease, chronic liver disease, asthma and epilepsy. Benefiting from our consideration of many outcomes, we were able to rank the health risks for diseases across organs, with the brain, lung, thyroid and heart being identified as organs affected by diseases most robustly associated with loneliness. We also extended the literature by demonstrating that diseases of the digestive and circulatory systems were the most frequent causes of hospitalization among people with loneliness. These observations corroborate a previous meta-analysis reporting that loneliness had a greater effect on mental health outcomes than on other outcomes[27]. Similarly, several systemic studies have shown that psychosocial stress factors are most strongly associated with mental

and behavioural disorders and diseases of the nervous, endocrine, circulatory, respiratory and digestive systems[28–31]. Furthermore, our study improves upon previous studies by employing a negative control approach to address the bias of unmeasured confounding variables, ultimately enhancing the quality of the causal inference[32]. In addition, our findings regarding associations between loneliness and several major disease categories (that is, diseases of the circulatory, digestive and nervous systems) were supported by results from two racially diverse cohorts, including individuals from the US and Chinese populations, which might help broaden the generalizability of our findings. Briefly, our study findings indicated that loneliness may be associated with adverse effects on physical and mental health[11].

Surprisingly, our outcome-wide MR analyses revealed non-causal associations between loneliness and most of the diseases considered. Although numerous observational studies have indicated that loneliness is associated with multiple diseases[12,14–17,19–21], reverse causality is an unavoidable concern in observational studies. Therefore, it has been debated whether loneliness is a causal risk factor or simply a surrogate marker for most diseases. Several previous studies using MR approaches have attempted to disentangle this puzzle[20,25,26]. Consistent with our findings, Abdellaoui, A. et al.[26] reported non-causal links between genetic liability to loneliness and most cardiovascular traits. In contrast, one recent MR study indicated a potentially causal association between loneliness and type 2 diabetes mellitus[20]. However, this study had several potential limitations, including overlapping samples and influence of the potential confounding effects of BMI and depressive symptoms, which may have biased the estimates away from the null hypothesis[20]. Taken together, we provided genetic evidence from MR analyses supporting non-causal associations between loneliness and a wider range of common physical diseases as tested in this study.

Nevertheless, we should interpret these negative results from the MR analyses cautiously due to the following possible considerations. First, the causal estimate from two-sample MR analyses may be biased towards the direction of the null due to the influence of weak instrumental variables. However, the *F*-statistics of all SNPs exceeded 20 ($F > 10$ being sufficiently strong), indicating that the inclusion of potential weak instrumental variables in the main analyses was unlikely[33]. Second, theoretically, the pleiotropy of SNPs might also lead to false negative results; however, pleiotropy typically biases the causal estimates away from the null in practice[34]. Therefore, the null finding in our MR analyses is more convincing evidence of a truly non-causal association. Third, loneliness was associated with a wide range of risk factors for poor health, such as alcohol use, sedentary behaviours and poor sleep[35]. Consistent with the literature[17,18], these socioeconomic and health behaviours indeed explained a substantial part of the associations between loneliness and diseases, as shown in our explanatory analyses. Furthermore, people with comorbidities, such as people with diabetes[15,36], depression[19] and hearing or vision impairments[37], were more likely to experience loneliness. Similar to the findings of previous studies[17,18], our explanatory analyses suggested that depressive mood and comorbidities might explain a large proportion of these associations between loneliness and diseases, especially between loneliness and mental and behavioural disorders. Although several sensitivity analyses were employed to address the potential confounding effects arising from comorbid depression or poor general health in the present study, the potential bias of reverse causality or residual confounding could not be completely eliminated[38]. Taken together, our MR findings on non-causal associations help clarify the existing debate by offering compelling evidence indicating that loneliness is potentially simply a surrogate marker rather than a causal risk factor for most diseases tested.

Several previous MR or genetic association studies have reported that feeling lonely is genetically correlated with several disease outcomes, especially mental outcomes such as depressive symptoms and general well-being[26,39], and that the associations of loneliness with depression[25] are potentially causal. In addition to these causal associations, we also found that loneliness is potentially causally associated with several other diseases, such as hypothyroidism, asthma, psychoactive substance abuse, sleep apnoea and hearing loss. Our study improved upon these existing MR studies by applying a meta-analysis of MR based on different source data, using more than 70 SNPs for the construction of instrumental variables, conducting negative control analyses and using LHC-MR methods, which jointly enhanced the evidence supporting the causal inference of associations between loneliness and diseases[20,25,26,39]. In addition, our TWAS results showed that genetic factors associated with loneliness were significantly expressed in organs or tissues, including the brain, visceral adipose tissue, thyroid and digestive system, further supporting our observations of causal associations.

Given the close genetic links between loneliness and depression[25], the causal inference of loneliness–disease associations may have been biased by genetic factors shared with depression. In line with two previous MR studies[26,39], we observed little evidence of causal associations of loneliness to heart diseases and obesity. However, we found potentially causal associations when accounting for genetic factors shared with depression. This finding may indicate that genetic factors shared with depression could have biased the results of the causal inference for some diseases, such as cardiometabolic diseases. To further address the potential influence of genetic factors shared with depression on other disease outcomes, we conducted several sensitivity analyses, including removing SNPs associated with depression, adjusting for the genetic liability to depression and employing the mtCOJO approach[40]. The results were largely consistent with the main analyses, suggesting that genetically causal associations between loneliness and most disease outcomes are unlikely to be solely attributable to genetic factors shared with depression[25].

Beyond being bridged by weakened overall health, loneliness might contribute to increased risk for diverse diseases through differential biological and genetic mechanisms. First, as a psychosocial stressor, loneliness may be associated with elevated stress responses, including overactivation of the neural alarm system, dysregulation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system activity[8,41]. These effects may underpin the robust associations between loneliness and some stress-related diseases, such as mental disorders and respiratory, digestive and cardiometabolic diseases. Second, increasing evidence supports the notion that loneliness is closely associated with elevated levels of inflammation[9]. Our results further supported that inflammation might account for some of the associations between loneliness and various diseases, especially inflammatory diseases such as rheumatoid arthritis, asthma and infections. Moreover, recent neuroscience research has reported that loneliness is characterized by reduced social reward associated with the suppression of dopamine neurons in the dorsal raphe nucleus[42], which may have bridged associations between loneliness and maladaptive behaviours or some behavioural disorders such as substance abuse.

The current findings have several public health and clinical implications. First, our findings on the non-causal associations between loneliness and most of the diseases tested suggest that only addressing loneliness is unlikely to reduce the risks of most diseases. Instead, our findings highlight the necessity of addressing the subsequent risk factors related to loneliness, including unfavourable lifestyle behaviours, depressive symptoms, or comorbidities, to improve health outcomes. However, our MR findings reinforce the idea that loneliness could be a pivotal and amenable target for preventing certain groups of diseases such as depression and substance abuse[43,44]. Overall, our study highlights the adverse health impacts of loneliness and supports recent statements that addressing the pandemic of loneliness is a public health priority[3,11].

The present study has several strengths, including a large sample size, a prospective design, consideration of a wide range of health

outcomes, consideration of bias from unmeasured confounding factors (that is, negative control approach and sensitivity analyses) and a stringent control of multiple comparisons. Another strength is that we conducted meta-analyses of two-sample MR approaches across two resources and carried out a subset of MR sensitivity analyses to provide robust genetic evidence supporting potential causal associations between loneliness and individual diseases across multiple systems.

However, the following limitations should be considered when interpreting these findings. First, selection bias may have arisen from the low response rate and outcome identification by electronic health or death registries to document diseases in the UK Biobank study. Nonetheless, previous analyses have suggested a close agreement between findings from the UK Biobank and representative UK samples for risk factor–disease associations[45]. Second, the measurement of loneliness included in the UK Biobank dataset is relatively crude due to two simple questions used in the UK Biobank, although these questions were derived from a validated UCLA scale[46] and recall bias may have led to an underestimation of loneliness. However, the definition of loneliness used here has been widely applied by several previous studies involving different cohorts[16,46]. Third, because a measure of loneliness at a single timepoint was used, we were unable to identify any time-varying associations. A meta-analysis of 76 observational studies suggested that the trajectory of loneliness among older people remains relatively stable[47], indicating that a single loneliness measurement could be an acceptable indication of long-term exposure in an observational cohort, even though loneliness could be changed or alleviated through interventions, such as multicomponent social interventions and resilience training[44], in older adults. Fourth, the negative control exposures selected in the present study may be imperfect. Nonetheless, the results from negative control outcome analyses, together with MR in our study, may still have provided sufficiently robust evidence for causal inference. Finally, the key findings in the current study were mainly derived from a European population. Therefore, caution should be taken when generalizing our findings to other ethnic groups.

Conclusions

This large prospective cohort study demonstrated that loneliness was associated with a greater risk of widespread diseases across 13 disease categories (30 out of 56 individual diseases), especially mental and behavioural disorders, infectious diseases, and diseases of the nervous, respiratory and endocrine systems. However, most of the observed associations between loneliness and diseases were not causal as suggested by the MR study. Multiple levels of risk factors or comorbidities may have contributed to most loneliness–disease associations. These observations collectively indicate that loneliness may serve as a potential surrogate marker, but not a causal risk factor for most of the diseases tested.

Methods

Study design and participants

The UK Biobank is a large population-based cohort study that included over 500,000 participants aged 37–73 years from 22 sites across England, Scotland and Wales between 2006 and 2010[48]. All the participants provided written informed consent. This study was approved by the National Health Service National Research Ethics Service (11/NW/0382). The present study included 476,100 participants from the UK Biobank for major analyses (Fig. 1 and Supplementary Method 1). The study also utilized data sourced from two independent population-based cohort studies, the CHARLS and HRS datasets, to support our results (Supplementary Method 2).

Exposures

In the UK Biobank cohort, loneliness was assessed using two questions administered by a touchscreen questionnaire; the questions were derived from the short-item UCLA Loneliness Scale[14]: (1) 'Do you often feel lonely?' (1 point = 'yes'; 0 point = 'no') and (2) 'How often are you able to confide in someone close to you?' (1 point = responding with 'never' or 'almost never'; 0 point = 'almost daily', '2–4 times a week', 'about once a week', 'about once a month' or 'once every few months'). The sum of the scores for these two questions (0–2 points) was considered as the loneliness index score. We further categorized the participants into two groups: loneliness (index score of 2) and no loneliness (index score of <2). In addition, the item 'feeling lonely' was assessed by the first question (scoring 1 point), and the item 'able to confide' was assessed using the second question (scoring 1 point). Details of the scoring methods are listed in Supplementary Method 3.

Outcomes

In the UK Biobank study, the incidence of disease categories and individual diseases was ascertained by linking hospital admission data and death registry records. The outcome-wide analyses included 14 disease categories and 56 individual diseases as the major outcomes, which were documented according to the International Classification of Diseases-10th Revision (ICD-10) codes (Supplementary Table 26). The data were accessible up to 12 November 2021. We calculated person-years from the date of entry to the UK Biobank to the date of death, first event or cessation, whichever occurred first. When one specific type of outcome occurred, we did not treat other outcomes as censored.

Covariates

We considered the following characteristics as potential covariates: age (continuous, years), sex (female/male), ethnicity (white/others), education level (college or university degree/non-college or university degree), employment (employed/unemployed), smoking status (never/previous/current), alcohol intake frequency (not current/two or less times a week/three or more times a week), BMI (continuous, kg m^{-2}) and physical activity (continuous, minutes per week). Detailed information is provided in Supplementary Method 4 and Supplementary Table 26.

Mendelian randomization

We conducted meta-analyses of bidirectional two-sample MR studies that used summary-level data extracted from genome-wide association studies (GWASs). Genetic instrumental variables for loneliness were derived from a GWAS conducted by the UK Biobank. Instrumental variables for the diseases were identified from two distinct GWAS datasets: the European Bioinformatics Institute (EBI) and the FinnGen consortium (Round 8). The details regarding the selection of genetic instrumental variables for loneliness and for each disease, along with detailed GWAS information, are described in Supplementary Method 5 and Supplementary Tables 27–29.

To investigate the bidirectional causal associations between genetic liability to loneliness and individual diseases, we focused our analyses on the 26 out of 56 diseases that were significant after Bonferroni correction in the Cox models and had appropriate GWAS data available. For each outcome analysis for loneliness and the selected diseases, we identified SNPs associated with each trait. For loneliness, we selected SNPs from the 97 included SNPs that were likely to directly affect individual diseases (that is, SNPs with $P < 5 \times 10^{-6}$ for each disease) and excluded them to ensure that the SNPs associated with loneliness would not directly influence the disease outcomes. Conversely, for each disease, we selected disease-associated SNPs and excluded any SNPs that directly influenced loneliness. Subsequently, we used ORs and their 95% CIs to assess the risks of individual diseases caused by loneliness and the effect of these diseases on loneliness, choosing the random-effects multiplicative inverse variance weighted (MRE-IVW) method as our primary analysis method for both directions[34].

To combine the MRE-IVW results from the FinnGen and EBI consortia, we employed the metagen function of the 'meta' package to

conduct a meta-analysis of the MRE-IVW results[49]. In the meta-analysis, we selected the Sidik–Jonkman (SJ) method (method.tau = 'SJ') to estimate heterogeneity[50], this method having been shown to have lower bias in previous simulation studies, particularly when heterogeneity variance is large[51]. We also used a random-effects model to assess the combined effect size and its statistical significance for each outcome. The meta-analysis for each outcome, including the OR, 95% CI, *P* values under the random-effects model and the heterogeneity statistic I^2, is reported. I^2 values <25%, 25–75% and >75% were considered to indicate low, moderate and high heterogeneity, respectively. In addition, we applied the Benjamini–Hochberg method to adjust the *P* values for multiple comparisons across all outcomes to ensure the accuracy and reliability of the statistical results[52].

To examine the robustness of the results of the MR studies and to identify possible horizontal pleiotropy, we performed several sensitivity analyses for both directions, including weighted median, ME-Egger, MR-PRESSO and LHC-MR analyses. In summary, the weighted median method can provide consistent causal estimates even when up to 50% of the genetic instrumental variables are ineffective[53]. Egger regression detects pleiotropy biases by analysing the regression intercept and can offer robust causal effect estimates even when all genetic variants may be ineffective[54]. The MR-PRESSO method effectively detects and corrects for potential outliers, and its global test assesses horizontal pleiotropy due to SNP estimate heterogeneity[55]. By modelling the effects of latent heritable confounders on complex traits, the LHC-MR method can effectively handle genetic confounders, enhance the accuracy of estimates and reduce estimation biases by accounting for sample overlap[56]. We also used Cochran's *Q* test to examine the heterogeneity of SNP estimates in each MR association. In addition, to minimize the influence of pleiotropy from depression on the causal association between loneliness and disease, we performed sensitivity analyses by removing any SNPs associated with depression ($P < 0.001$), conducting multivariable MR analyses correcting for genetic liability to depression and BMI by using GWAS data from the FinnGen consortium and using mtCOJO analyses adjusted for depression[40]. We also performed a negative control MR analysis using individual loneliness GWAS data from the UKB population (Supplementary Method 5).

To confirm the predicted gene expression changes in tissue and organ systems, we also conducted a TWAS analysis on the loneliness data by using the MR-Joint Transcriptome Imputation (MR-JTI) method (Supplementary Method 6).

Statistical analyses

Continuous baseline characteristics are presented as the mean (s.d.) or mean (IQR) if continuous. Any missing data were multiply imputed using the 'mice' R package to maximize statistical power, under the assumption that the data were randomly missing. For the analysis of various outcomes, we used Cox proportional hazards models to calculate HR and 95% CI to evaluate the associations of loneliness and each item with the incidence of multiple diseases in each independent cohort study. The multivariate Cox models were adjusted for age, sex, ethnicity, education level, employment status, smoking status, alcohol intake frequency, BMI and physical activity. We also performed multiple comparisons (70 tests) using the Bonferroni correction[57], and a $P < 7.14 \times 10^{-4}$ was considered to indicate statistical significance. We calculated the PAF using Levin's formula[58], which determines the proportion of disease cases that could be avoided by eliminating loneliness among the population. To examine the long-term disease burden, we calculated the cumulative incidence per 1,000 persons for disease categories among individuals with loneliness in the UK Biobank study.

Negative control on exposure and outcome studies were performed to address bias of unmeasured confounding factors. Although our negative control analyses were not pre-registered and thus primarily exploratory, they were based on two reasonable previous assumptions: (1) 'zero causality': exposures or outcomes of the control should not be causally associated with the exposures or outcomes of interest; (2) 'U-comparable': exposures or outcomes of control should share a similar confounding structure with the exposures or outcomes of interest[32,59]. On the exposure side, we accordingly selected 'frequency of travelling from home to job workplace' and 'usual side of head for mobile phone use' as two potential negative control exposures from a long list of personal factors assessed at baseline within the UK Biobank. These factors are likely to share similar bias structures with loneliness and to meet the 'U-comparable' assumption. To our knowledge, there is no existing evidence supporting causal associations between these two items and most of the disease outcomes of interest, indicating that these two variables are also likely to meet the 'zero causality' assumption. On the outcome side, similar to a previous study[60], we selected 'injury in transport accident' as a negative control outcome because it is unlikely to be causally associated with loneliness. Detailed information on the negative control analyses is provided in Supplementary Method 7 and Supplementary Fig. 3.

Several other sensitivity analyses were conducted to examine the robustness of the major findings of this analysis. First, we excluded participants with missing covariate data. Second, we excluded any events occurring within the first 2 years. Third, we calculated the Fine–Gray subdistribution hazards and incorporated death as a competing risk of incident diseases to investigate the potential bias from competing risks. Fourth, we further adjusted for social isolation. Finally, we excluded participants with long-standing illness, disability or infirmity, and participants with self-reported depressive symptoms.

Subgroup analyses were conducted by dividing the sample according to age (<60 years or ≥60 years), sex (male or female) and obesity status (underweight or normal, overweight or obese). The *P* values for the interactions among loneliness, multiple diseases and stratification variables were used to determine the significance of the interactions.

To evaluate the degree to which explanatory factors accounted for the associations between loneliness and multiple diseases, we calculated the PERM for the following six categories of explanatory variables (details are shown in Supplementary Fig. 4): (1) socioeconomic factors: education level, Townsend Deprivation Index and employment; (2) health behaviours: health diet score, smoking status, alcohol intake frequency, sleep duration and physical activity; (3) metabolic factors: BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose and low-density lipoprotein cholesterol (LDL-C); (4) baseline depressive symptoms; depression scores measured using the Patient Health Questionnaire-2 (PHQ-2); (5) inflammatory factors: leucocytes, platelets, platelet crit, lymphocytes, monocytes, neutrophils, eosinophils, basophils, C-reactive protein; and (6) comorbidities: history of long-standing illness, use of diabetes medication, use of cholesterol-lowering medication and use of antihypertensive medication. Briefly, for each group of explanatory factors, we estimated the PERM as follows[17]:

$$\mathrm{PERM} = \left[\frac{\begin{array}{c}\mathrm{HR\,(age,\ sex,\ ethnicity,\ assessment\ centre\ adjusted)} - \\ \mathrm{HR\,(age,\ sex,\ ethnicity,\ assessment\ centre,\ and\ explanatory\ factors\ adjusted)}\end{array}}{\mathrm{HR\,(age,\ sex,\ ethnicity,\ assessment\ centre\ adjusted)} - 1} \right] \times 100\% \quad (1)$$

mtCOJO analyses were performed using GCTA software v.1.94.1, whereas other statistical analyses were performed using R v.4.3.1. Specific R packages and their versions used included: the mice package (v.3.16.0) for data imputation; the survival package (v.3.5.7) for performing Cox proportional hazards regression; the TwoSampleMR package (v.0.5.7) for conducting two-sample Mendelian randomization analysis; the MRPRESSO package (v.1.0) for performing MR-PRESSO

analysis; the lhcMR package (v.0.0.0.9000) for LHC-MR analysis; the meta package (v.7.0.0) for meta-analysis; and the ggplot2 package (v.3.4.4) and forestplot package (v.3.1.3) for data visualization.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Individual-level data from the UK Biobank are not publicly available due to their policy, but the data will be made available after the application of the UK Biobank (https://www.ukbiobank.ac.uk/). CHARLS is freely available to the public, and researchers can directly apply for data access on the website (http://charls.pku.edu.cn/). HRS datasets are available publicly at the University of Michigan Institute for Social Research. To access them, researchers need to submit a data user agreement to the HRS team (https://hrs.isr.umich.edu/data-products). The GWAS data used in the MR study were sourced from the UK Biobank (UKB), the European Bioinformatics Institute (EBI) and the FinnGen consortium (Round 8, except for BMI data, which are from Round 9 due to absence in Round 8). The loneliness data from the UK Biobank (UKB) are sourced from the IEU Open GWAS project. Detailed information and access to the resource are available at https://gwas.mrcieu.ac.uk/. Data from EBI can be accessed at https://www.ebi.ac.uk/gwas/. Details and access to the data from the FinnGen consortium (Round 8) are available at https://www.finngen.fi/en/access_results.

Code availability

Scripts utilized for conducting the analyses can be accessed via GitHub at https://github.com/Mingqingzhou/R-codes (ref. 61).

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Author contributions

All authors met the authorship criteria, and no others meeting the criteria were omitted. All authors reviewed and approved the final paper. Jihui Zhang, L.Q. and Y.Y.L. conceived of the study. S.A., M.Z. and Y.H. contributed to the statistical analyses, with the help of W.Z. and Q.W. S.A., T.L., F.J. and Jun Zhang helped with the software and modified the methods. Y.Y.L. had the primary responsibility of writing the paper, with the help of S.A., M.Z., Y.H., F.J. and Jun Zhang. All authors provided comments and helped revise the paper. Jihui Zhang had full access to all data in the study. Jihui Zhang, S.A. and L.Q. supervised the study.

Competing interests

The authors declare no competing interests.

Additional information

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Software and code

Policy information about availability of computer code

Data collection	In this study, no software was used to collect data
Data analysis	mtCOJO analyses were performed using GCTA software (version 1.94.1), and other analyses were conducted using R (version 4.3.1). Specific R packages and their versions included: mice package (version 3.16.0) for data imputation; survival package (version 3.5.7) for performing Cox proportional hazards regression; TwoSampleMR package (version 0.5.7) for conducting two-sample Mendelian randomization analysis; MRPRESSO package (version 1.0) for performing MR-PRESSO analysis; lhcMR package (version 0.0.0.9000) for LHC-MR analysis; meta package (version 7.0.0) for meta analysis; ggplot2 package (version 3.4.4) and forestplot package (version 3.1.3) for data visualization. Scripts utilized for conducting the analyses can be accessed via https://github.com/Mingqingzhou/R-codes.

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Individual-level data from the UK Biobank are not publicly available due to their policy, but the data will be made available after the application of the UK Biobank (https://www.ukbiobank.ac.uk/). As for the CHARLS, it is freely available to the public, and researchers can directly apply for data access on the website (http://charls.pku.edu.cn/). HRS datasets are available publicly at the University of Michigan Institute for Social Research. To access them, researchers need to submit a data user agreement to the HRS team (https://hrs.isr.umich.edu/data-products). The GWAS data used in the MR study were sourced from the UK Biobank (UKB), the European Bioinformatics Institute (EBI), and the FinnGen consortium (Round 8, except for BMI data, which is from Round 9 due to the absence in Round 8). The loneliness from the UK Biobank (UKB) is sourced from the IEU Open GWAS project. Detailed information and access to the resource is available at the respective websites: https://gwas.mrcieu.ac.uk/. Data from EBI can be accessed at their official website https://www.ebi.ac.uk/gwas/. Details and access to the data from the FinnGen consortium (Round 8) are available at https://www.finngen.fi/en/access_results.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	In our study, we accounted for sex in our analyses. For example, in the databases from the UK Biobank, the China Health and Retirement Longitudinal Study (CHARLS), and the Health and Retirement Study (HRS), we adjusted for sex using Cox proportional hazards models. Furthermore, in the UK Biobank, we performed gender-stratified subgroup analyses. Sex was determined based on self-reported data collected through questionnaires, and all participants provided written informed consent to share their individual-level data.
Reporting on race, ethnicity, or other socially relevant groupings	In our study, we used socially constructed or socially relevant classification variables such as ethnicity, education level, employment status, smoking status, alcohol intake frequency, and BMI. These variables were chosen due to their relevance to the research question and their potential influence on the study outcomes. We adjusted for these variables in the Cox proportional hazards models and conducted sensitivity analyses to evaluate the robustness of our results. The careful selection and control of these variables ensured the validity and reliability of our findings. The information on these variables was self-reported by participants through questionnaires.
Population characteristics	This study primarily analyzed data from 476,100 participants (age range, 38-73 years; median follow-up, 12.2 years) from the UK Biobank. To enhance the robustness and generalizability of our findings, we replicated the main analyses in two independent population-based cohort studies: the China Health and Retirement Longitudinal Study (N = 15,924; age range, 22-101 years; median follow-up, 5.8 years) and the Health and Retirement Study (N = 14,056; age range, 50-108 years; median follow-up, 7.5 years). Baseline demographic data of participants are presented in Table 1 and Supplementary Tables 1-2. We calculated descriptive statistics as mean (SD) for continuous variables and number (percentage) for categorical variables.
Recruitment	In the UK Biobank study, a subset of 502,505 participants was invited to complete touchscreen questionnaires between 2006 and 2010. Out of these, 476,100 participants with valid and complete data on loneliness were included in our analysis. For the China Health and Retirement Longitudinal Study (CHARLS), the initial baseline recruitment in 2011 included 17,596 participants. After excluding 1,672 individuals with missing data on loneliness, the final sample consisted of 15,924 participants. In the Health and Retirement Study (HRS), we initially assessed 19,193 participants. We excluded 4,828 participants with invalid loneliness data and 309 participants who were under the age of 50, leaving a final sample size of 14,056 participants.
Ethics oversight	The UK biobank was approved by the National Health Service National Research Ethics Service (11/NW/0382). All the participants provided written informed consent. This research was conducted using the UK Biobank Resource under application number 93604. The ethical approval for CHARLS was granted by the Institutional Review Board of Peking University (IRB00001052-11015), and all participants provided written informed consent. The HRS is supported by the National Institute on Aging (NIAU01AG009740) and the Social Security Administration. All participants provide written informed consent before each interview.

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Sample size	To ensure the validity of our study and maximize the sample size for sufficient statistical power, we undertook the following steps:I n the UK Biobank, from the initial 502,505 participants, we excluded 26,206 individuals with missing loneliness data and 139 individuals who had withdrawn from the study, resulting in a final sample size of 476,160 participants for analysis. In the China Health and Retirement Longitudinal Study (CHARLS), out of the initial 17,596 participants, we excluded 1,672 individuals with missing loneliness data, leaving a final sample of 15,924 participants for analysis. For the Health and Retirement Study (HRS) database, we started with 19,193 participants. After excluding 4,828 individuals with missing loneliness data and an additional 309 individuals who were younger than 50 years old, we were left with a final sample size of 14,056 participants for analysis.
Data exclusions	In the three databases (the UK Biobank, the China Health and Retirement Longitudinal Study (CHARLS), and the Health and Retirement Study (HRS)), we excluded participants with missing loneliness data, those with corresponding diseases at baseline, participants who withdrew, and participants under the age of 50 in the HRS
Replication	We conducted primary analysis in the UK Biobank and replicated the analysis in the China Health and Retirement Longitudinal Study (CHARLS) and the Health and Retirement Study (HRS). The results from CHARLS and HRS databases were largely consistent with those from the UK Biobank.
Randomization	This is an observational cohort study, and randomization is not applicable in this study
Blinding	Blinding was not applicable to this study as it is observational in nature.

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Plants

Seed stocks	This study does not involve the use of seed stocks or other plant materials.
Novel plant genotypes	The methods for producing novel plant genotypes were not applicable in this study
Authentication	Authentication procedures were not applicable as no novel genotypes were generated in this study. Additionally, experiments assessing the effects of mutations were not conducted.