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Social isolation, loneliness, and multi-system medical conditions: phenome-wide association and disease-trajectory analyses

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Abstract

Background Social isolation and loneliness have emerged as important modifiable risk factors for mental disorders, posing significant public health challenges. However, they have not been comprehensively investigated in relation to multisystemic diseases and their temporal trajectories. We aimed to systematically identify the health outcomes associated with social isolation and loneliness and characterize their disease trajectories and comorbidity networks.

Methods A total of 466,547 participants (mean age: 56.5 ± 8.1, 54.6% females) with available information on social isolation and loneliness were included from the UK Biobank between 2006 and 2010 and followed up until 2022. Social isolation was measured using a composite score derived from three questions on number in household, frequency of friend and family visits, as well as participating in leisure and social activities. Loneliness was assessed by the subjective perception of feeling lonely and the willingness to confide in others. A total of 246 medical conditions were included in phenome-wide association analyses. Disease trajectory and comorbidity network analyses were performed to identify sequential patterns and visualize disease clusters.

Results During an average medium follow-up of 11.7 years, social isolation was found to be significantly associated with increased risks of 28 medical conditions, and loneliness with 80. The strongest association for both exposures was with personality disorders, with respective hazard ratios of 2.12 (95% CI, 1.59–2.82) for social isolation and 2.62 (95% CI, 1.90–3.61) for loneliness. The conditions covered a broad spectrum, including respiratory, neurological, digestive, musculoskeletal, and genitourinary diseases and mental disorders. Three main disease clusters were identified in relation to social isolation and eight disease clusters were related to loneliness. Septicemia and alcohol-related disorders as the initial condition was notably observed in the disease cluster trajectories of both social isolation and loneliness. Subsequently, the comorbidity network revealed three and five distinct comorbidity modules associated with social isolation and loneliness, respectively. The disease nodes within these modules exhibited structural consistency with those within the disease trajectory clusters.

Conclusions These findings highlight the importance of integrating screening, interventions, and referrals for social isolation and loneliness into health care system to prevent the adverse health conditions.

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Keywords Social isolation, Loneliness, Disease trajectory, Disease cluster, Network analysis

Background

Social isolation is defined as the objective insufficiency in both the quantity and frequency of social interactions within relationships [1, 2]. Loneliness, on the other hand, refers to the subjective adverse emotion experienced when an individual perceives a distressing feeling of solitude or being socially isolated due to a discrepancy between their expected and perceived social relationships [3, 4]. Existing epidemiological studies have demonstrated that social isolation and loneliness are prevalent health concerns across all age groups. Among community-dwelling older populations, approximately 25% experience social isolation [5], with similar rates observed in Europe where 24.2% of older adults report loneliness [6]. In middle-aged and younger demographics, studies have documented loneliness rates ranging from 1.8% to 12.0%, specifically reaching 4.2% among middle-aged adults [5]. Recent evidence further reveals elevated prevalence in younger generations [7, 8], particularly those under 40 years old, where reported loneliness levels significantly increased during the COVID-19 pandemic [9]. These consistent findings across age strata underscore the multigenerational nature of loneliness as a public health challenge. Social isolation and loneliness may co-occur frequently, but not always. Both independently contribute to the risks of poorer mental health [10] and premature death [11]. This is not solely attributed to the severe social isolation caused by the public health crises. More critically, newly occurring life events or changes in individuals' resilience to painful events [12], and environmental and structural transformations in workplace, familial, and community settings have collectively exacerbated feelings of loneliness [13, 14]. Concurrently, the prevailing trends of individualism and urban migration have diminished opportunities for providing and receiving support within community or intergenerational settings [15]. Pervasive short-sighted and negligent decision-making in society reinforces prejudices and structural discrimination, fostering lonelygenic environments in which many experience persistent isolation and insecurity [16]. These factors collectively contribute to the profound impact of social isolation and loneliness on health issues, which persists throughout individuals' life courses.

Given the persistently high prevalence of social isolation and loneliness over the past several decades, the health consequences of the issues have attracted widespread research attention. The accumulating evidence suggests that persistent social isolation and loneliness are associated with an increased risk of various psychiatric disorders [17–20] (e.g., depression, anxiety, schizophrenia, and suicide) and somatic diseases (e.g., cardiovascular disease [CVD] [21, 22], type 2 diabetes [23], dementia [24], and certain infectious diseases [25]). However, previous studies have primarily focused on specific disease groups, and there has been a lack of comprehensive investigation into the overall impact of social isolation and loneliness on multiple medical conditions. A comprehensive analysis of disease trajectories following the occurrence of social isolation and loneliness could facilitate the identification of key pathways connecting social isolation and loneliness with subsequent medical conditions [26].

Emerging cohort studies integrate population-level electronic health records data, apply comorbidity strength measures to filter significant disease pairs, and validate temporal precedence through binomial testing to establish the potential directionality of disease progression. Subsequent nested case–control designs quantified disease–disease associations using regression modeling, while trajectory network visualizations identified sequences of diagnoses subsequent to psychiatric disorders [27, 28]. The population-wide disease trajectory analysis could be utilized as a promising tool for elucidating the potential progression and trajectory network of social isolation and loneliness-related disease clusters throughout an individual's lifespan. To address the current lack of research in this field, we aimed to investigate the multi-system medical conditions associated with social isolation and loneliness in a large-scale population-based cohort. By visualizing disease trajectories and elucidating the magnitude and temporal patterns of disease–disease associations, we further characterize the key affected pathways leading to general health deterioration associated with social isolation and loneliness (Fig. 1).

Methods

Study population

The UK Biobank, a large-scale community-based prospective cohort study, recruited over 500,000 participants aged 37–73 years from 22 assessment centers across the UK between 2006 and 2010 [29]. Participants completed touchscreen questionnaires, attended physical measurements, and provided blood samples at recruitment centers.

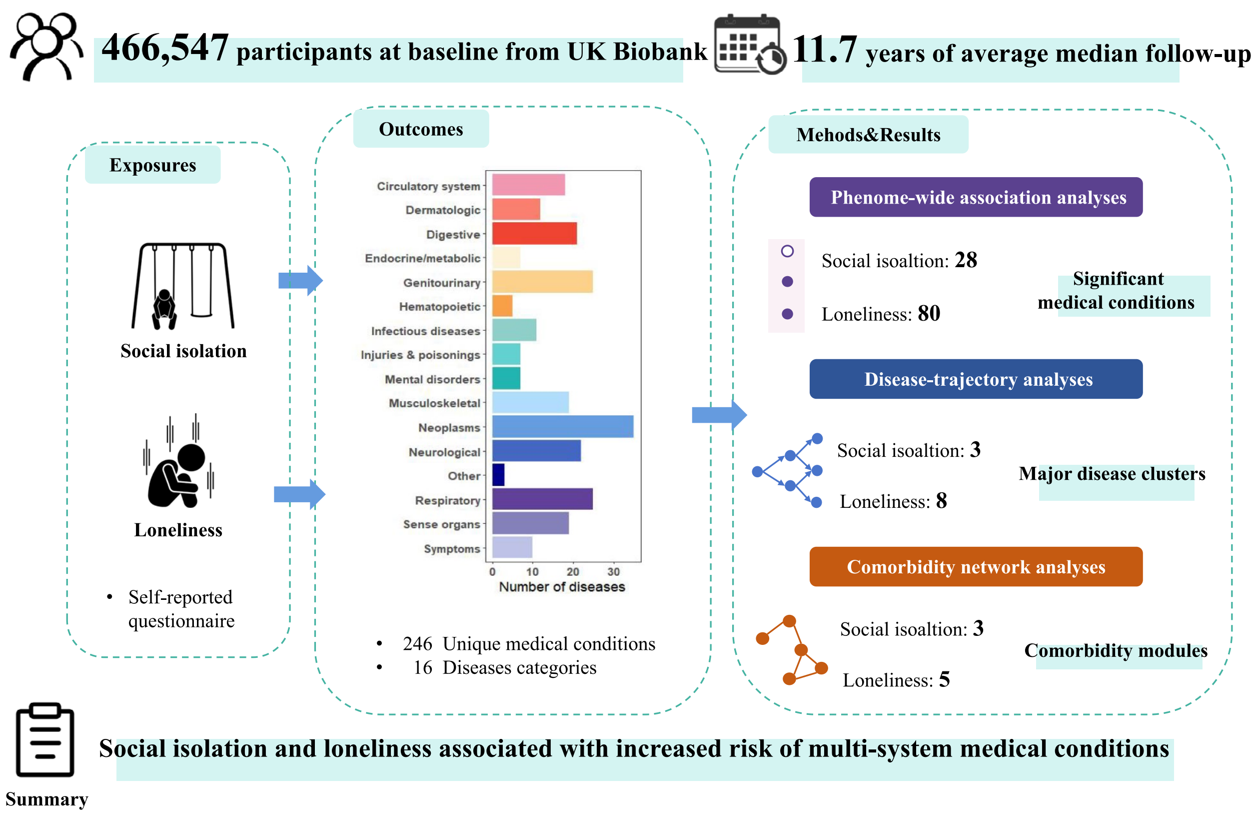

Fig. 1 Summary of the study. The present study included 466,547 participants from the UK Biobank. Baseline social isolation and loneliness were assessed using composite scores derived from 3-item and 2-item self-reported questionnaires, respectively. A total of 246 unique medical conditions from 16 phecode categories were obtained through the UK Biobank inpatient hospital data. During an average medium follow-up of 11.7 years, the phenome-wide association study (PheWAS) identified 28 and 80 medical conditions significantly associated with social isolation and loneliness, respectively. Disease trajectory and comorbidity network analyses revealed three disease trajectory clusters and three distinct comorbidity modules associated with social isolation, and eight clusters and five modules linked to loneliness

In the present study, we excluded participants who had missing data or responded “prefer not to answer” or “do not know” regarding questionnaires on social isolation and loneliness ($n = 35{,}854$). A total of 466,547 individuals with complete data were ultimately included in the primary analysis. Follow-up commenced at baseline recruitment and continued until either death, loss to follow-up, or the end of the study (31 October 2022), whichever occurred first.

Assessment of social isolation and loneliness

The assessment of social isolation primarily focuses on objective social connections and was derived from the following three questions, similar to the validated Berkman-Syme social network index [30]: (1) “How often do you visit friends or family or have them visit you?” (1 point for the response of “once a month,” “once every few months,” “never or almost never,” or “no friends or family outside the household”); (2) “Which of the following leisure or social activities do you engage in once a week or more often? You may select more than one of them: sports club or gym, pub or social club, religious group, adult education class, or other group activities” (1 point for the response of “none of above”); and (3) “Including yourself, how many people live in your household?” (1 point for the response of “1”).

The assessment of loneliness focuses on the subjective perception of social isolation and consisted of two questions derived from the revised University of California, Los Angeles loneliness scale [31]: “Do you often feel lonely?” (1 point for the response of “yes”) and “How often are you able to confide in someone close to you?” (1 point for the response of “never or almost never”).

We utilized the scoring methodology employed in previous studies to establish a comprehensive social isolation score ranging from 0 to 3 and a total loneliness score ranging from 0 to 2 [22, 32]. Higher scores on these scales indicate greater levels of social isolation and loneliness, respectively. Participants were categorized as experiencing social isolation if their social isolation score was ≥ 2 (on a scale of 0–3), and as experiencing loneliness if their loneliness score reached the maximum threshold of 2 (on a scale of 0–2).

Ascertainment of medical conditions

The health-related conditions were obtained by regular linking to national electronic health-related datasets. Inpatient hospital data, covering all UK Biobank participants since 1997, were periodically updated from the Hospital Episode Statistics database, the Scottish Morbidity Record, and the Patient Episode Database in England, Scotland, and Wales [29]. The diagnosis of each participant's medical conditions was identified based on the main and secondary diagnoses linked to inpatient hospital data according to the International Classification of Diseases-Tenth Revision (ICD-10).

In the present study, we restricted the phenome-wide association analyses (PheWAS) to chapters 1–14 of the ICD-10 codes [27], excluding chapters related to pregnancy and perinatal conditions, congenital malformations, deformations and chromosomal abnormalities, symptoms or signs, specific consequences of external causes, external causes of morbidity and mortality, as well as factors influencing health status. The PheCODE schema was then used to define phenotypes by mapping the remaining ICD-10 codes to "phecodes" (Additional file 1: Table 1) [33]. This coding system is considered more relevant to diseases discussed in clinical settings and widely used in PheWAS [34]. To ensure statistical power, PheWAS analysis was only performed for 246 top-level phecodes corresponding to 3-digit ICD-10 codes and with no less than 200 cases to ensure statistical power [35]. For each medical condition, the date of diagnosis was defined as the date of the first hospital visit with a diagnosis of the corresponding phecode. The diagnostic accuracy of medical conditions in the UK Biobank inpatient hospital data have been validated to be 80.3% (interquartile range, 63.3–94.1%) through a comparison between routinely collected data sets and case notes [36].

Ascertainment of covariates

The following characteristics were selected as covariates that were considered potentially confounding in previous studies [32, 37]. Sociodemographic status included age (in years), sex (female/male), ethnicity (white/others), Townsend deprivation index (TDI, continuous variables obtained from the residential postcode, with a higher score indicating a greater degree of deprivation), employment status (employed/unemployed), and educational attainment (college or university degree/non-college or university degree, including A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, and other professional qualifications such as nursing or teaching). Lifestyles characteristics included height (cm, continuous), weight (kg, continuous), smoking status (never/previous/current), alcohol intake status (never/previous/current), diet score (continuous variable constructed to reflect dietary patterns based on the frequency of consuming fruits, vegetables, fish, processed meat, unprocessed red meat, whole grains, and refined grains, with higher scores indicating a healthier dietary pattern [38]), self-reported sleep duration (in hours per day), and physical activity (continuous variable representing metabolic equivalent task-sum [MET] of hours engaged in light-, moderate-, and vigorous-intensity activities on an average day). The missing covariates were coded as a missing indicator category for categorical variables and with mean values for continuous variables.

Statistical analyses

Mean and standard deviation (SD) were used to describe continuous variables, and numbers (percentages) to describe categorical variables. Baseline characteristics of participants included sociodemographic status (age, sex, ethnicity, TDI, employment status, and educational attainment) and lifestyles behaviors (height and weight, smoking status, alcohol intake status, diet score, sleep duration, and physical activity) were compared based on different status of social isolation and loneliness. We used the χ^2 test for categorical variables, or analysis of variance or Mann–Whitney *U* test for continuous variables, as appropriate.

Phenome-wide association analysis (PheWAS)

We performed a phenome-wide association study (PheWAS) using multivariable Cox proportional hazards models, implemented with the R package survival (version 3.8–3), to separately examine the associations of social isolation and loneliness (analyzed in independent models) with a wide range of medical conditions. Each model was adjusted for potential confounders, including age, sex, ethnicity, employment status, educational attainment, TDI, height and weight, smoking status, alcohol intake status, diet score, sleep duration, and physical activity. To reduce reverse causality, we excluded participants who had a prior diagnosis of the medical condition under investigation, as well as those who developed the condition within the first 2 years of enrollment. Additionally, we excluded the follow-up time during the first 2 years for all participants. For each association tested, we calculated a false discovery rate-adjusted *P* value (*FDR-P*) to account for multiple testing. The proportional hazards assumptions were tested based on Schoenfeld residuals. Given our focus on identifying conditions with increased risk linked to social isolation and loneliness, only associations with both an *FDR-P* < 0.05 and a hazard ratio (HR) > 1 were retained for further analyses, including disease trajectory and comorbidity network construction.

Disease trajectory analyses

To explore the temporal sequence of disease progression, three sequential critical steps were integrated to establish and combine disease pairs, thereby constructing sequential trajectories. (1) Comorbidity pair identification. We first constructed all possible disease pairs as Disease 1 (D1) and Disease 2 (D2) from the identified medical conditions in the PheWAS results, calculated as $n^*(n-1)$, and focused our analysis only on disease pairs that co-occurred with a prevalence of at least 1.0% among participants who reported social isolation or loneliness. The comorbidity strength between each disease pair was quantified by using both relative risk (RR) and the Φ-correlation [27, 39]. Disease pairs showing significant comorbidity strength (RR > 1.0 and Φ-correlation > 0, and *FDR-P* < 0.05) were retained for further analysis. (2) Temporal order validation. To identify disease pairs with a logical temporal order, we conducted a binomial test to determine whether a significantly greater number of individuals were diagnosed with D2 subsequent to D1, compared to the reverse order, among those who received both D1 and D2 diagnoses. (3) Association quantification. For each disease pair (D1 to D2) with a confirmed temporal order, we constructed nested case–control datasets within sub-cohorts by considering D2 as the outcome and D1 as the exposure variable. We then used conditional logistic regression models to validate the association between D1 and D2, while adjusting for the same set of confounders utilized in the PheWAS analysis. Finally, significant disease pairs were interconnected via a shared disease to construct disease trajectory networks associated with social isolation or loneliness Notably, the progression from D1 to D2 and subsequently from D2 to D3 can be integrated into a continuous trajectory represented as D1 to D2 to D3.

Comorbidity network analyses

In parallel, we performed comorbidity network analyses without considering the temporal direction between diseases. For each disease pair with significant comorbidity (as defined above), we used unconditional logistic regression models to estimate the strength of association, adjusting for the same confounders. Pairs with confirmed positive associations (OR > 1 and *FDR-P* < 0.05) were included in the comorbidity network. To identify clusters of highly interconnected diseases, we applied the Louvain algorithm for community detection using the R package igraph (version 2.1.4). This algorithm is well-suited for partitioning networks into modules based on high internal connectivity [40]. The structure of the disease trajectory and comorbidity networks is illustrated in Additional file 1: Fig. S1.

Subgroup and sensitivity analyses

We performed subgroup analyses to investigate whether the effects of social isolation or loneliness on medical conditions could be influenced by gender. Furthermore, to minimize the potential for inferential bias, we repeated PheWAS in the sample with excluded missing covariates data.

All the statistical analyses were performed using the R software (version 4.3.3), and all disease trajectories were visualized using Cytoscape (version 3.9.0). For multiple testing, an *FDR-P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics

During an average medium follow-up of 11.7 years, the PheWAS included 466,547 participants, with females accounting for 54.6% of the sample. The average age was 56.5 years and the majority identified as white ethnicity (91.5%). A total of 66,897 participants reported social isolation, and 29,418 participants were identified as experiencing loneliness; both were included in subsequent disease trajectory and comorbidity network analyses, respectively. As shown in Table 1, participants experiencing social isolation were more likely to be male, whereas loneliness was more common in females. These groups exhibited more unhealthy lifestyle behaviors, including higher proportions of current smokers, irregular sleep patterns, lower diet scores, and fewer average weekly hours of physical activity.

Phenome-wide association analysis (PheWAS)

We finally defined 246 unique medical conditions with more than 200 cases, defined into 16 phecode classes. After adjusting for potential confounders, the PheWAS analysis identified 28 medical conditions positively associated with social isolation (Fig. 2; Additional file 1: Table 2). These significant medical conditions were predominantly concentrated in the disease categories of mental disorders, respiratory diseases, and dermatologic and neurological diseases. Personality disorders showed the highest HRs (HR, 2.12; 95% CI, 1.59–2.82); next was anxiety disorders (HR, 1.72; 95% CI, 1.27–2.35). Furthermore, a total of 80 medical conditions showed statistically significant (*FDR-P* < 0.05) increased risks with loneliness, focusing on the disease categories of respiratory diseases, neurological diseases, symptoms, digestive diseases, musculoskeletal diseases, genitourinary and

Table 1 Baseline characteristics categorized based on experiencing of social isolation and loneliness

Characteristics[a]	Total (*N* = 466,547)	Social isolation			Loneliness		
		No socially isolated (*n* = 399,650)	Socially isolated (*n* = 66,897)	*P* value	No loneliness (*n* = 437,129)	Loneliness (*n* = 29,418)	*P* value
Age (years), mean (SD)	56.5 (8.1)	56.6 (8.1)	56.1 (7.9)	< 0.001	56.6 (8.1)	55.9 (7.9)	< 0.001
Sex, female	254,711 (54.6)	221,445 (55.4)	33,266 (49.7)	< 0.001	239,330 (54.8)	15,381 (52.3)	< 0.001
Ethnicity, white	427,077 (91.5)	367,545 (92.0)	59,532 (89.0)	< 0.001	400,683 (91.7)	26,394 (89.7)	< 0.001
TDI, mean (SD)	− 1.4 (3.0)	− 1.5 (2.9)	− 0.4 (3.4)	< 0.001	− 1.4 (3.0)	− 0.4 (3.4)	< 0.001
Currently employed	273,709 (58.7)	232,255 (58.1)	41,454 (62.0)	< 0.001	257,545 (58.9)	16,164 (54.9)	< 0.001
College or university degree	153,659 (32.9)	131,368 (32.9)	22,291 (33.3)	0.022	146,341 (33.5)	7318 (24.9)	< 0.001
Weight (kg), mean (SD)	78.1 (15.9)	77.9 (15.7)	79.2 (16.9)	< 0.001	77.9 (15.8)	80.3 (17.5)	< 0.001
Height (cm), mean (SD)	168.5 (9.2)	168.5 (9.2)	168.9 (9.4)	< 0.001	168.5 (9.2)	168.2 (9.4)	< 0.001
Current smoker	48,503 (10.4)	37,691 (9.4)	10,812 (16.2)	< 0.001	43,410 (9.9)	5093 (17.3)	< 0.001
Current drinker	431,171 (92.4)	371,980 (93.1)	59,191 (88.5)	< 0.001	404,978 (92.6)	26,193 (89.0)	< 0.001
Diet score[b]	3.9 (1.5)	3.9 (1.4)	3.8 (1.5)		3.9 (1.4)	3.6 (1.5)	
Sleep duration				< 0.001			< 0.001
6–8 h/day	60,614 (13.0)	49,813 (12.5)	10,801 (16.1)		54,578 (12.5)	6036 (20.5)	
< 6 or > 8 h/day	405,933 (87.0)	349,837 (87.5)	56,096 (83.9)		382,551 (87.5)	23,380 (79.5)	< 0.001
Summed MET hours per week for all physical activity	44.3 (41.0)	45.0 (41.0)	39.7 (40.5)	< 0.001	44.3 (40.8)	43.2 (43.1)	< 0.001

SD standard deviation, *TDI* Townsend deprivation index, *MET* metabolic equivalent task

[a] All characteristics were presented as means (SD) or *n* (percentage)

[b] Diet score was summarized by using the following food categories: fruits: ≥ 3 servings/day, vegetables: ≥ 3 servings/day, fish: ≥ 2 servings/week, processed meats: ≤ 1 serving/week, unprocessed red meats: ≤ 2 servings/week, whole grains: ≥ 3 servings/day, refined grains: ≤ 2 servings/day, with higher scores indicating a healthier dietary pattern

circulatory system diseases, dermatologic and infectious diseases, mental disorders, and sense organ disease. Subsequent somatic diseases with the strongest associations with loneliness were personality disorders (HR, 2.62; 95% CI, 1.90–3.61), adjustment reaction (HR, 2.37; 95% CI, 1.57–3.58), other demyelinating diseases of central nervous system (HR, 2.18; 95% CI, 1.23–3.87), and anxiety disorders (HR, 2.01; 95% CI, 1.39–2.92) (Fig. 2; Additional file 1: Table 3).

Disease trajectories and comorbidity network related to social isolation

Based on significant medical conditions confirmed by PheWAS, we further identified 20 disease pairs among 378 possible disease pairs according to the comorbidity strength measures and 16 diseases pairs with clear temporal orders. These disease pairs were further used to construct disease trajectories and comorbidity networks related to social isolation (Additional file 1: Tables 4 and 5). Figure 3A presents the overview of the disease trajectories related to social isolation; we observed 3 major disease clusters that emerged as a series of medical conditions following the diagnosis of diseases ordered as D1. Cluster 1, which originated from septicemia in infectious diseases, developed two subsequent evolutionary trajectories through the disease node of other anemias. One trajectory directly led to chronic airway obstruction, subsequently developing into pleurisy and pleural effusion as well as constipation, and ultimately progressed to the downstream urinary tract infection. The other trajectory progressed to tobacco use disorders, then relied on dual pathways involving chronic airway obstruction and constipation to evolve downstream into urinary tract infection. Clusters 2 and 3, derived from alcohol-related disorders and pneumonia respectively, demonstrated progression patterns that overlapped with cluster 1 through the intermediate disease nodes of tobacco use disorders and chronic airway obstruction.

The comorbidity patterns identified based on 20 disease pairs related to social isolation were visualized by comorbidity modules in the comorbidity network analyses (Fig. 3B). Employing the Louvain algorithm, we divided the social isolation-associated comorbidity network into 3 distinct modules. Importantly, we observed a significant structural alignment between the aggregation of related disease nodes in these modular partitions and sequential disease progression patterns within clinical trajectories. The middle upper module, for instance,

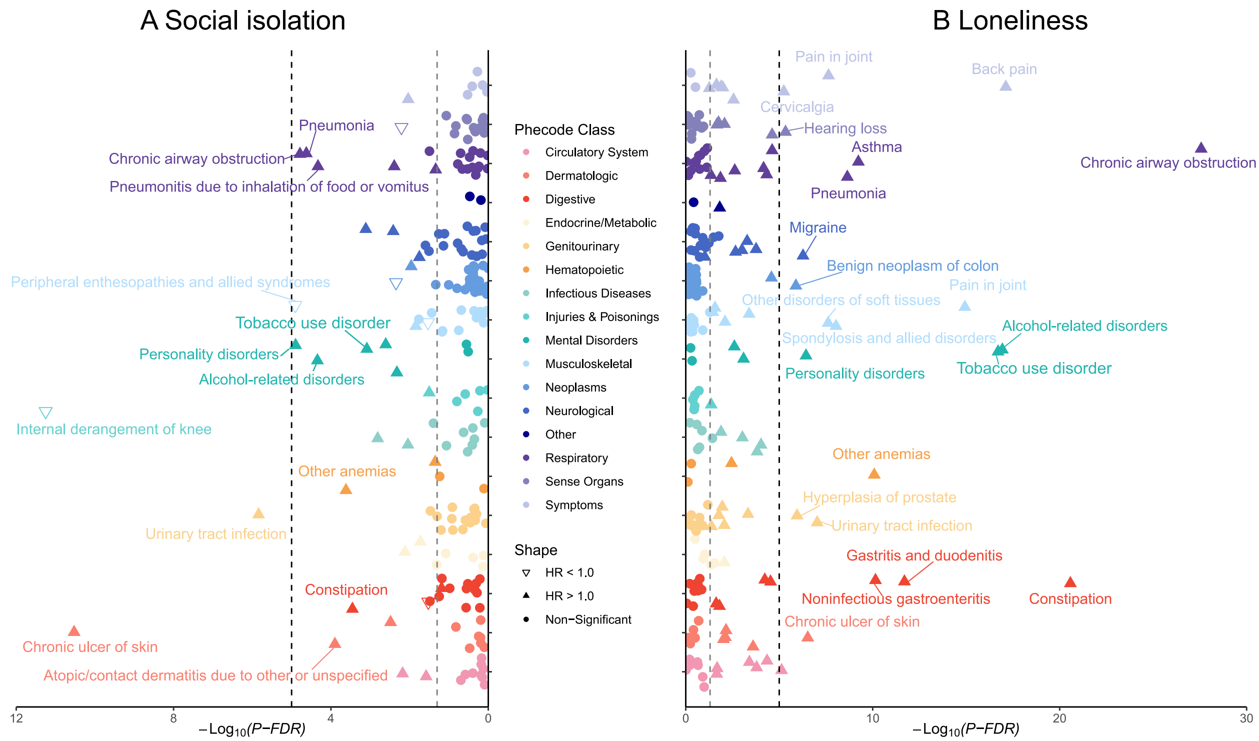

Fig. 2 The associations between social isolation and loneliness with the risk of 246 medical conditions. The x-axis corresponds to the logarithms of the FDR-adjusted *P* values derived from the PheWAS, with larger values indicating higher statistical significance. The gray dashed line denotes the statistical significance threshold (*FDR-P* < 0.05). Each dot or triangle represents a medical condition, solid upward-pointing triangles indicate positive associations (HR > 1.0), hollow downward-pointing triangles denote inverse associations (HR < 1.0), and dots represent non-significant associations. Medical conditions are colored according to their respective phecode classes. Abbreviations: *FDR* false discovery rate, *PheWAS* phenome-wide association analyses

exhibited characteristic clustering patterns manifesting as interconnected relationships among two disease categories: respiratory disorders (i.e., pneumonia, pleurisy and pleural effusion, and chronic airway obstruction) and digestive diseases (i.e., constipation). This combinatorial disease aggregation pattern demonstrates remarkable consistency with the progressive clinical trajectory identified in social isolation-associated disease cluster 3.

Disease trajectories and comorbidity network related to loneliness

In total, 66 disease pairs with clear temporal orders were established among all 3160 possible disease pairs related to loneliness (Additional file 1: Table 6). As shown in Fig. 4A, 8 major clusters that the first-layer diseases (ordered as D1) in the network leading to more subsequent medical conditions were observed. Similar to the disease trajectory network associated with social isolation, other anemias in hematopoietic diseases emerged as critical intermediate nodes mediating numerous downstream medical conditions within the loneliness-related disease trajectory network. For instance, cluster 1 (initiated with septicemia) and clusters 3–4 (both originating from neoplasms) demonstrated trajectory clusters that proliferated after passing through other anemias, mediating multiple diseases including respiratory diseases (e.g., pneumonia, asthma), digestive diseases (e.g., gastritis and duodenitis, constipation), genitourinary diseases (e.g., urinary tract infection, hyperplasia of prostate), and symptoms (e.g., back pain, pain in limb). Cluster 5 exhibited shared progression patterns derived from alcohol-related disorders and encompassed more medical conditions compared to cluster 2 of social isolation-related trajectories. Clusters 6 and 8, originating from other peripheral nerve disorders and spondylosis and allied disorders respectively, both displayed progression pathways where back pain development subsequently resulted in limb pain. Cluster 7 commenced with cataract from sense organ diseases, progressing predominantly through asthma and constipation before culminating in hyperplasia of prostate.

A total of 94 disease pairs with strong comorbidity strength were further used to constructed comorbidity networks related to loneliness and partitioned into

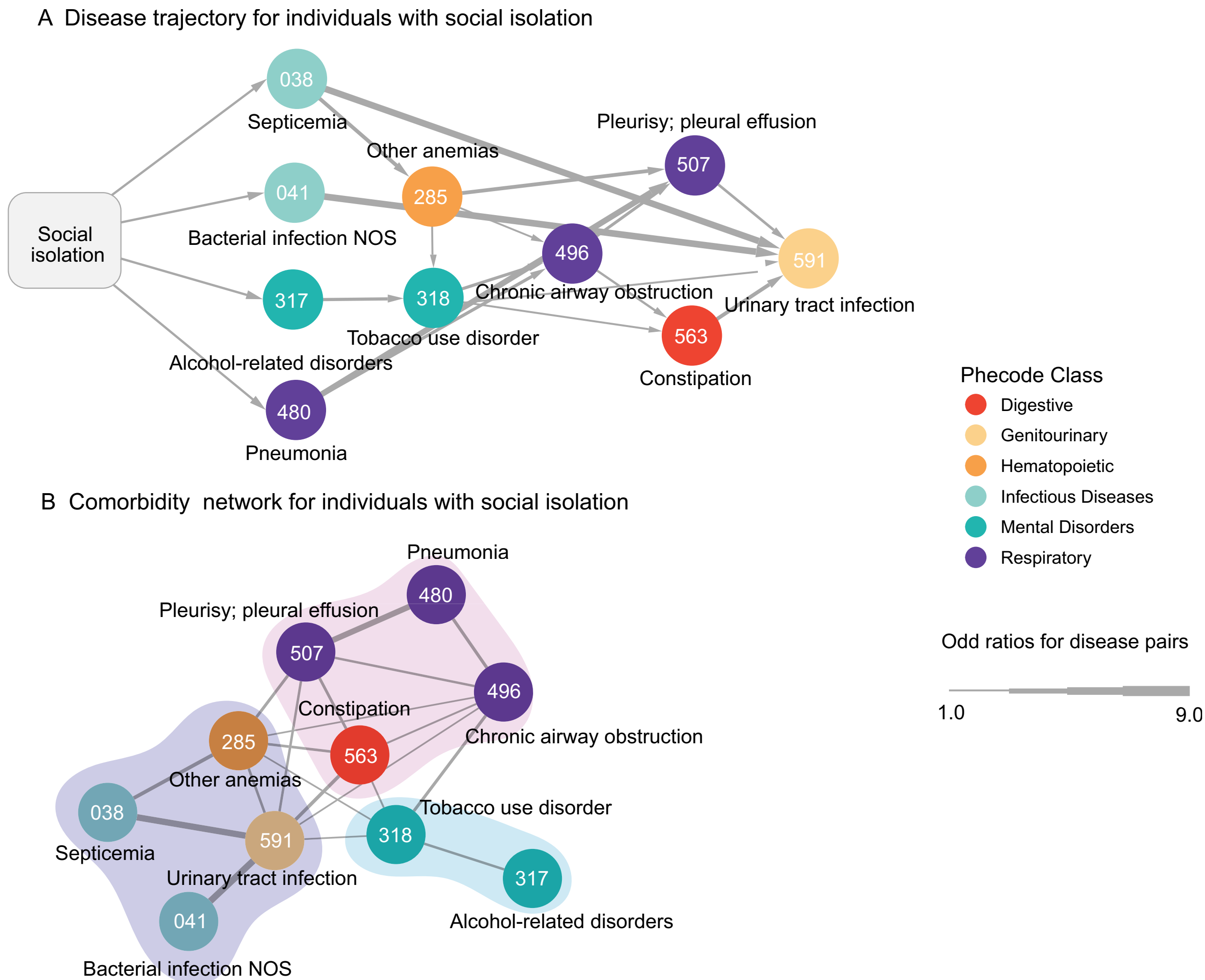

Fig. 3 The temporal disease trajectories and comorbidity networks related to social isolation. Each node represents a medical condition and is labeled with its name and "phecode," colored according to the phecode class to which it belongs. **A** Disease trajectory for individuals with social isolation. Arrows indicate the direction of association between disease pairs (D1 to D2, e.g., 480 to 496) validated by binomial testing. Arrow width represents the strength of temporal associations, quantified by ORs derived from adjusted conditional logistic regression analyses using nested case–control data with D2 as the outcome and D1 as the exposure. Disease trajectory clusters are defined as initial diseases (e.g., 480) sequentially connecting to multiple subsequent conditions (496, 507, 563, 591). **B** Comorbidity network for individuals with social isolation. Nodes with non-temporal associations (e.g., 480 and 507) are connected by links. The width of the link denotes the comorbidity association strength measured by ORs from adjusted unconditional logistic regression. The network is partitioned into 3 modules using the Louvain algorithm, with nodes belonging to the same module aggregated within corresponding color-highlighted regions. Abbreviation: *ORs* odd ratios

5 modules (Fig. 4B, Additional file 1: Table 7). Notably, the middle upper module was observed to be structurally similar to the disease node aggregation in the loneliness-associated disease trajectories of cluster 1 and cluster 2, demonstrating interconnections among disease nodes from infectious diseases, digestive diseases, genitourinary diseases, and hematopoietic and musculoskeletal diseases. Concurrently, the middle lower module, which included a series of respiratory disease and mental disorders, was consistent with the disease nodes of cluster 5.

Subgroup and sensitivity analyses

The subgroup analysis of PheWAS by gender revealed a higher number of associated subsequent diseases associated with social isolation and loneliness in male compared to female (Additional file 1: Tables 8 and 9). Specifically, social isolation was positively associated with 13 medical conditions among female. In contrast, social isolation was significantly associated with a higher risk for 14 medical conditions in male. Regarding loneliness, we found similar differences in the association patterns between females and males, with

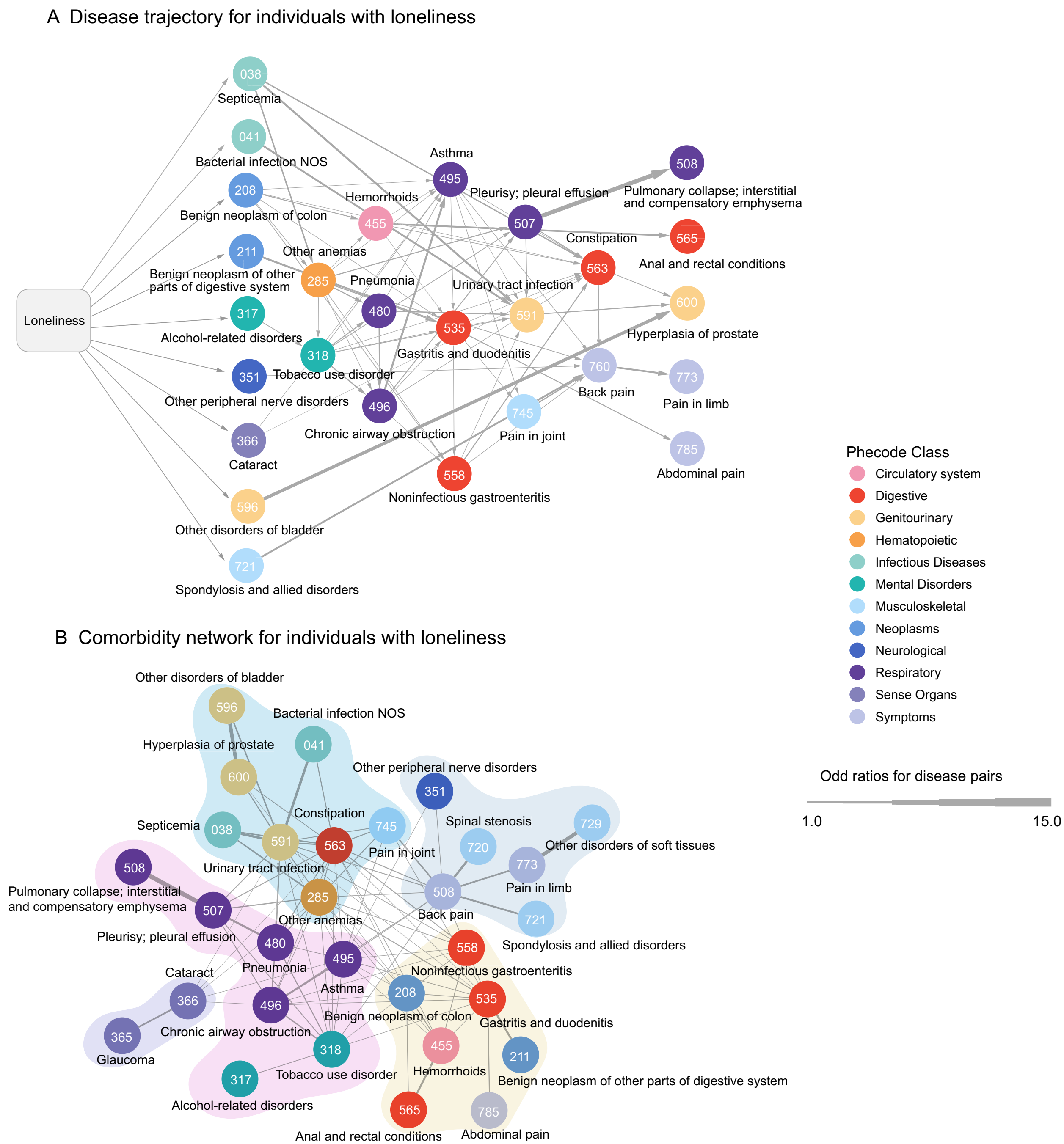

Fig. 4 The temporal disease trajectories and comorbidity networks related to loneliness. Each node represents a medical condition and is labeled with its name and "phecode," colored according to the phecode class to which it belongs. **A** Disease trajectory for individuals with loneliness. Arrows indicate the direction of association between disease pairs (D1 to D2, e.g., 721 to 760) validated by binomial testing. Arrow width represents the strength of temporal associations, quantified by ORs derived from adjusted conditional logistic regression analyses using nested case–control data with D2 as the outcome and D1 as the exposure. Disease trajectory clusters are defined as initial diseases (e.g., 721) sequentially connecting to multiple subsequent conditions (760, 773). **B** Comorbidity network for individuals with loneliness. Nodes with non-temporal associations (e.g., 596 and 600) are connected by links. The width of the link denotes the comorbidity association strength measured by ORs from adjusted unconditional logistic regression. The network is partitioned into 5 modules using the Louvain algorithm, with nodes belonging to the same module aggregated within corresponding color-highlighted regions. Abbreviation: *ORs* odd ratios

52 and 55 medical conditions respectively associated with loneliness. Largely similar result patterns were observed in the repeated analysis, where individual's missing values on covariates were excluded (Additional file 1: Tables 10 and 11).

Discussion

In the present study, we comprehensively examined associations between social isolation and loneliness and multisystemic medical conditions in a large community-based cohort. Social isolation correlated with elevated risks of 28 conditions, while loneliness linked to 80 conditions, primarily involving mental disorders, respiratory diseases, and dermatologic and neurological diseases. Disease trajectory analysis has confirmed three major disease clusters related to social isolation, and eight disease clusters related to loneliness based on the similarity of potential affected systems or etiology. Poor mental health, behavior-related changes (such as alcohol and tobacco abuse), and impaired immune function may serve as key pathways connecting social isolation and loneliness with a wide range of other medical conditions downstream. The comorbidity network revealed three social isolation-associated modules and five loneliness-associated modules with high intrinsic connectivity, particularly showing structural overlap between their disease nodes and those identified in disease trajectory clusters. Collectively, these findings may help to illustrate the comprehensive health impacts of social isolation and loneliness, underscoring the imperative to prioritize coordinated prevention strategies for multimorbidity in public health agendas.

Although no studies have provided comprehensive assessments on health consequences associated with social isolation and loneliness, our results gain support from accumulated evidence consistently indicating positive associations between social isolation or loneliness and various health conditions. Consequently, there remains a significant knowledge gap regarding the relationship between social isolation and loneliness and other subsequent systemic somatic diseases from the perspective of data-driven, hypothesis-free approach. The findings of the PheWAS study were substantiated by analyzing inpatient hospital data from the UK Biobank. This comprehensive analysis encompassed 246 distinct medical conditions across 16 phecode categories, revealing significant associations of social isolation and loneliness with a broad spectrum of mental and physical illnesses and disorders. Our analyses confirm that social isolation and loneliness are associated with a subsequently increased risk of developing individual psychiatric disorders. A previous review highlighted the prominent presence of prosocial behaviors in humans and their protective effects on health and adaptation [41]. However, when individuals experience exclusion and fall into the distressing state of loneliness or isolation, it will be associated with a wide range of psychiatric disorders such as mood disorders, psychosis, and drug dependence [42, 43]. Furthermore, some additional Mendelian randomization (MR) studies have provided estimates of the causal effects of these positive relationships [44, 45]. In contrast to previous studies primarily focused on consistently reporting associations with common major chronic conditions like cancer and CVD, our analyses also revealed associations of social isolation and loneliness with an elevated risk of subsequent individual diseases, including respiratory diseases, digestive diseases, infectious diseases, and pain symptoms. In summary, these findings reveal positive associations of social isolation and loneliness with overall health decline and, more importantly, elucidate the evolutionary patterns of subsequent health outcomes.

In visualizing disease trajectories and comorbidity networks, we identified a series of key nodes in the individual progression patterns of social isolation and loneliness across medical conditions. For example, appearing in the first layer of the disease trajectory network are septicemia and alcohol-related disorders, which dominated the beginning of the disease tree gram and carried many diseases downstream. Previous evidence has demonstrated that social isolation and loneliness often concurrently impact multiple organ systems [46], with several biological, psychological, and behavioral mechanisms proposed as drivers of the health effects associated with social isolation and loneliness. Firstly, exposure to social isolation and loneliness triggers persistent activation of the hypothalamic–pituitary–adrenal (HPA) axis and leads to alterations in glucocorticoids levels [47, 48], an elevated proinflammatory response [49], and oxidative stress [50]. When these pathological processes persist over a prolonged period of experiencing social isolation or loneliness, they negatively impact a wide range of physiological functions including glucose metabolism, apoptosis, immune responses, reproductive health, cardiovascular systems as well as inflammation production, thus compromising homeostasis [47]. Secondly, the psychological pathways encompassing different psychological factors have been identified to partially explain the association between loneliness with adverse health outcomes [51]. These factors include perceived stress [52] and depression [21] which contribute significantly to the detrimental effects on health. Thirdly, lack of companionship from partners contributes to a higher prevalence of unhealthy behaviors among individuals experiencing social isolation or loneliness by reducing the likelihood of maintaining non-smoking habits or abstaining from alcohol consumption. It also hampers healthy dietary choices as well as engagement in physical exercise [53] and undermines adherence to prescribed medications [54], thereby exacerbating the occurrence of adverse outcomes. Taken together, based on the network of disease trajectories associated with social isolation and loneliness, we can hypothesize that prolonged exposure to cumulative distressing emotions and chronic psychological stress in lonely and socially isolated individuals increases susceptibility to alcohol and tobacco abuse and weakens immune function (potentially through immunosuppression). These changes ultimately lead to the subsequent emergence of a range of somatic diseases.

From a public health perspective, our findings highlight the urgency of implementing targeted interventions for individuals experiencing social isolation or loneliness. A recent review summarized two categories of intervention targets for social isolation and loneliness [55]. The first category involves strategies specifically aimed at reducing social isolation and loneliness as primary outcomes. These approaches include enhancing social skills, providing social support, and increasing opportunities for social interaction at the individual level. Concurrently, community network resources and sociopolitical policies are necessary to facilitate the incorporation of interventions targeting social disconnection across diverse ethical and cultural contexts [13, 56]. The second category focuses on improving non-social isolation and loneliness outcomes in the lives of individuals experiencing social isolation and loneliness, potentially emphasizing the prevention of adverse health consequences such as enhancing nutritional status and promoting healthier behaviors. As revealed by the trajectory network analysis in this study regarding the pathways through which social isolation and loneliness interact with various medical conditions, these measures could provide sustainable indirect health benefits for affected individuals. However, it must be pointed out that in the global public health crisis of loneliness, the elderly population, as a high-risk group, will see a near doubling of the proportion of individuals aged over 65 years within the next 30 years [57]. Although remote and in-person interventions have been proposed to reduce the impact of social isolation and promote social connectedness among the elderly, their implementation is often complex. A particular challenge is matching services to the specific needs of patients, which requires input and coordination from a diverse set of siloed stakeholders [58]. Meanwhile, patient care and health information are fragmented across primary care, community, and public health organizations, and the lack of coordination and limited flow of information hampers service access for those who need it most [59].

Therefore, bridging these gaps requires a fundamental shift from a reactive focus on individualized care to a proactive, system-level approach that builds structurally connected communities. These efforts may include policy changes that promote social integration, for instance, zoning reforms that encourage the development of multigenerational housing communities. Furthermore, sustaining free or low-cost community programming through public grants can provide vital opportunities for social engagement across all age groups. Specifically, to address the needs of vulnerable aging populations, policy measures aimed at reducing the financial burden of assisted living facilities are crucial. Additionally, creating structured social programs that bridge generational divides, such as those connecting K-12 youth with older adults aged 65 and above, can simultaneously combat loneliness among the elderly while fostering empathy and social skills among the young, constituting a powerful preventive strategy.

Main strengths of our study include the inclusion of a large population-based cohort and the prospective collection of long-term and complete follow-up data. Furthermore, by utilizing PheWAS combined with disease trajectory and comorbidity network analyses, we identified several disease clusters, enhancing the reliability of connectivity between diseases within each cluster and their temporal sequence, and provided a comprehensive visualization of the overall patterns of subsequent health outcomes associated with social isolation and loneliness for the first time. There are several limitations that should be noted. First, social isolation and loneliness in the UK Biobank were assessed through several simple questions using incomplete scales. Although these questions were adapted from validated scales [30, 31], it must be acknowledged that the lack of objective social network indicators limited our ability to capture the structural dimensions of social isolation, potentially leading to underestimation of exposure. Simultaneously, the self-report methodology inherently carries risks of misclassification bias due to recall bias in retrospective assessments. However, these scales have been widely used in several previous studies across diverse cohorts [21, 22, 25, 60], demonstrating their validity in population-based studies. Future studies should still consider employing more objective social network indicators or combining multiple data sources to mitigate these biases. Second, the handling of missing covariates using missing indicators and mean imputation, while pragmatic for this study, has limitations. The preferred method, multiple imputation, provides more accurate standard errors by accounting for the uncertainty in missing values [61]. However, it was unsuitable here because it produces multiple datasets, which are computationally intensive and technically incompatible with our downstream trajectory and network analyses, as these require a single, consistent input dataset [62]. Third, the PheWAS analysis was limited to medical conditions with ≥ 200 cases, and due to the miss information, we unable to fully utilize the first occurrence data in the UK Biobank, which may have resulted in the exclusion of less severe and other medical conditions in our analysis. Therefore, it is necessary to validate the results of this study by using more extensive data sources for disease cluster identification. Furthermore, our analysis intentionally excluded inverse associations that may signify protective effects, as these fell outside our focus on mapping health deterioration pathways; however, exploring the mechanisms of comorbidity mitigation may also be of public health significance for future studies. Fourth, despite considering various confounding factors such as sociodemographic and lifestyle factors, and conducting time-lag analyses to mitigate reverse causation in the analysis, the observational nature of this study precludes complete elimination of residual confounding and the influence of subclinical or undiagnosed conditions on the associations between social isolation, loneliness, and disease risk. Future studies leveraging causal inference methods such as MR with genetic proxies for loneliness are needed to address these limitations. Further, it is challenging to investigate how time-varying confounders, such as behavioral factors, for which we had little information about would have contributed to the observed disease networks. Fifth, although our aim was to explore changes in health outcomes subsequent to social isolation and loneliness, disease trajectory analyses does not provide a sufficient basis for causal inferences by itself, while also providing support for causal relationships for future studies. Yet, the observed patterns might also be explained by the shared etiological factors between social isolation and loneliness and these conditions, including genetic, lifestyle, and other environmental factors. Lastly, the analysis of structural correspondence between disease clusters and network modules related to social isolation and loneliness, based on visualized disease trajectory and comorbidity network data, currently relies on visual inference. Future studies should prioritize developing systematic methods to statistically validate the robustness of these relationships.

Conclusions

In summary, we found that social isolation and loneliness are significantly associated with increased risk of a large number of physical and mental disorders. Disease trajectory and comorbidity network analysis identified multiple disease trajectories exposed to social isolation and loneliness, and depicted comorbidity networks with high intrinsic connectivity. These findings emphasize the potential benefits of early implementation of effective and systematic interventions to strengthen social connections and alleviate social isolation and loneliness for population health.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
FDR-P	False discovery rate-adjusted *P* value
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard ratio
ICD-10	International Classification of Diseases, Tenth Revision
MET	Metabolic equivalent of task
MR	Mendelian randomization
OR	Odds ratio
PheWAS	Phenome-wide association study
RR	Relative risk
SD	Standard deviation
TDI	Townsend deprivation index
UK	United Kingdom

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04555-4.

Additional file 1. Table 1 Mappings of ICD-10 codes to the phenotypes identified by phenome-wide association analyses (PheWAS). Table 2 Phenome-wide association analyses (PheWAS) results for social isolation in the UK Biobank. Table 3 Phenome-wide association analyses (PheWAS) results for loneliness in the UK Biobank. Table 4 Odds ratios (ORs) with 95% confidence intervals (CIs) for the significant disease pairs among individuals with social isolation in the trajectory analysis in the UK Biobank. Table 5 Odds ratios (ORs) with 95% confidence intervals (CIs) for the significant disease pairs among individuals with social isolation in the comorbidity analysis in the UK Biobank. Table 6 Odds ratios (ORs) with 95% confidence intervals (CIs) for the significant disease pairs among individuals with loneliness in the trajectory analysis in the UK Biobank. Table 7 Odds ratios (ORs) with 95% confidence intervals (CIs) for the significant disease pairs among individuals with loneliness in the comorbidity analysis in the UK Biobank. Table 8 Phenome-wide association analyses (PheWAS) results for social isolation in the UK Biobank among females and males. Table 9 Phenome-wide association analyses (PheWAS) results for loneliness in the UK Biobank among females and males. Table 10 Phenome-wide association analyses (PheWAS) results for social isolation in the UK Biobank by excluding participants with missing values in covariates. Table 11 Phenome-wide association analyses (PheWAS) results for loneliness in the UK Biobank using by excluding participants with missing values in covariates. Fig. S1 Flowchart of disease trajectory and comorbidity network analyses.

Additional file 2.

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Authors' contributions

TD and ZC conceived, designed, conduct of the study and the analysis and interpretation of the results, and wrote the first draft of the manuscript; ZC and CX conceived, designed, conduct of the study and the analysis and interpretation of the results and secured funding; TD, ZC, XW, TS, YW and CX have made critical revisions to the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors; CX is the guarantor of this work. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by NHS National Research Ethics Service (NW/0382). Patients/participants provided their written informed consent to participate in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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