nature portfolio

Peer Review File

Association of Loneliness Social Isolation and Healthy Lifestyle with Life Expectancy Free of Major Diseases

Corresponding Author: Professor Lu Qi

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Reviewer #3

(Remarks to the Author)
The authors did a great job on estimating the joint association of loneliness and social isolation with chronic-disease free life expectancy using data from UK biobank by sex. They also assessed if the association differs by healthy lifestyle factors. They found that loneliness and social isolation are associated with shorter life expectancy and lifestyle factor interacted with social loneliness.

1. Was the death information used in the analysis all-cause death or death caused by the 7 chronic diseases of interest? If it was all-cause death, would it introduce some bias when calculating disease free life expectancy? Would the competing risk overestimate the life expectancy you estimated?
2. Could you clarify when the healthy lifestyle was collected? Was it measured at the same time as exposure at baseline?
3. In the Statistical analysis section, you mentioned “To investigate whether the loss of disease-free years due to loneliness or SI could be mitigated by adopting a healthy lifestyle”. It sounds like healthy lifestyle is a mediator and you aimed to estimate the proportion of indirect effect among the total effect to me while you were estimating the interactive effect of loneliness/SI with healthy lifestyle. Could you rephrase it and throughout the paper to avoid confusion?
4. Instead of combining lifestyle and exposure into a new variable, do you consider adding the product term between exposure and healthy lifestyle in your model to assess how the association would change in different levels of healthy lifestyle? This could also help quantify how the lifestyle would interact with exposure on the outcome and test the significance.

Reviewer #4

(Remarks to the Author)
The study by Wang and colleagues examined the association between loneliness, social isolation, and LE free of physical and mental disease. They found loneliness and social isolation are more strongly associated with LE free of mental disease than with LE free of physical disease. Interestingly, they also found the loss of disease-free LE associated with social isolation narrowed with increasing levels of healthy lifestyle, but the loss of disease-free LE associated with loneliness did not. The novelty of the article is the inclusion of mental health in the calculation of disease-free life expectancy. This assessment of "aging" is very similar to the concept of “healthy aging”, but it provides a more intuitive means of assessment. I have some comments that may improve the importance of this study.

1. The authors included a total of 277,489 participants from the UK Biobank. To allow for replication of the results, the manuscript would benefit from including a flow chart of sample selection.
2. To get a general idea of the follow-up length, please provide at least the median (IQR).
3. How did authors deal with the missing data on covariates? Please declare the number or percentage for missing covariates.

4. Table 1 summarized only the average minutes of physical activity across exposure groups. How about the percentage of low or high-risk lifestyle factors?
5. I wonder whether there is a significant interaction between social isolation and loneliness on life expectancy or on the risk of mortality

Version 2:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
I think the authors for addressing my comments.

Reviewer #3

(Remarks to the Author)
The authors have addressed all my comments and I am happy with the current version of the manuscript.

Reviewer #4

(Remarks to the Author)
The authors have addressed the previous comments well and have notably strengthened the manuscript. The clarity of the analyses and presentation has improved.Nevertheless, I have several comments that I believe would further strengthen the manuscript.

The "Multistate Life Table" approach relies on the Markov assumption (the future state depends only on the current state, not the history). Was this assumption tested? Please briefly mention how you addressed or validated this (e.g., by testing for time-dependent effects of loneliness/SI in the Cox models used to generate transition hazards). If not tested, this should be noted as a potential limitation.

For the joint analysis of loneliness/SI and lifestyle, the sample size in some strata (e.g., "lonely + healthy lifestyle") might be small, potentially affecting the precision of the life expectancy estimates. Please provide the number of participants in each joint category (e.g., in a supplementary table) to reassure readers about the stability of these estimates.

A major limitation is the use of baseline-only assessments for loneliness, SI, and lifestyle. These factors are dynamic and likely change over a follow-up period of 13 years. Please emphasize this more strongly in the limitations section, as it may lead to non-differential misclassification and an underestimation of the true associations.Additionally, could the online follow-up questionnaires provided by UK Biobank help address this issue?

The sentence regarding sensitivity analysis ("excluding participants who became ill or died within two years") is clear. However, please explicitly state the rationale for choosing a 2-year landmark period.

Version 3:

Reviewer comments:

Reviewer #4

(Remarks to the Author)
No further comments.

Reviewers' comments:

Reviewer #3 (Remarks to the Author):

The authors did a great job on estimating the joint association of loneliness and social isolation with chronic-disease free life expectancy using data from UK biobank by sex. They also assessed if the association differs by healthy lifestyle factors. They found that loneliness and social isolation are associated with shorter life expectancy and lifestyle factor interacted with social loneliness.

[Response]
We greatly appreciate the Reviewer's encouraging and constructive comments. The Reviewer's comments and suggestions are very insightful and useful, and we have carefully revised our manuscript accordingly. Please kindly find the point-by-point responses as follows.

1. Was the death information used in the analysis all-cause death or death caused by the 7 chronic diseases of interest? If it was all-cause death, would it introduce some bias when calculating disease free life expectancy? Would the competing risk overestimate the life expectancy you estimated?

[Response]

Thank you very much for your valuable comments! In multistate lifetable method, only all-cause mortality is utilized to estimate disease-free life expectancy. A competing risk arises when individuals are at risk of multiple events, and the occurrence of one event (death) can prevent the occurrence of others (disease). If our analysis considers only **Transition 1 (from non-disease to incident disease)**, competing risks could be accounted for. However, multistate lifetable needs to consider 3 transitions simultaneously (**Transition 2: from non-disease to death; Transition 3: from disease diagnosis to death, please see Figure below**). **If we further accounted for the competing risk of death in Transition 1, the information on death would have been considered repeatedly, which is already included in transition 2.** Thus, we think it may not be appropriate to re-consider the competing risk of death in transition 1 when calculating the disease-free life expectancy using multistate lifetable method. The multistate lifetable method used in this study has been widely used in previous studies and is well-established within the academic community (*JAMA Intern Med. 2023 Apr 1;183(4):340-349.; BMJ. 2020*

Jan 8:368:l6669.; Arch Intern Med. 2007 Jun 11;167(11):1145-51.).

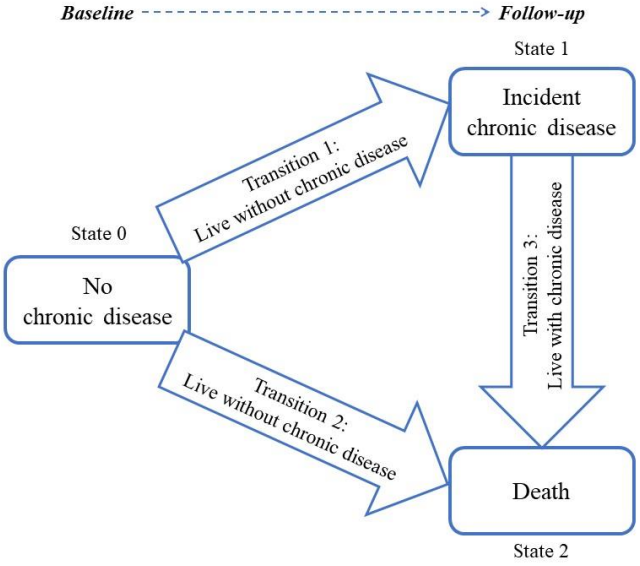


Diagram 1, Schematic diagram for three transitions over the time of follow-up.

In addition, as your suggestions, we performed the analysis to consider the competing risk of death in Transition 1. We observed that the results were very similar before and after accounting for competing risk of death. Please see the Table below:

Table. HR for transition 1 before and after considering competing risk of death

Model	HR (95% CI)			
	No loneliness or SI	Loneliness only	SI only	Loneliness and SI
7 Major Chronic Disease				
Original model	1 (reference)	1.16 (1.12, 1.20)	1.08 (1.05, 1.11)	1.22 (1.14, 1.31)
Model considering competing risk of death	1 (reference)	1.16 (1.12, 1.20)	1.08 (1.05, 1.11)	1.22 (1.14, 1.31)
5 Major Chronic Disease				
Original model	1 (reference)	1.09 (1.05, 1.14)	1.07 (1.04, 1.10)	1.15 (1.07, 1.24)
Model considering competing risk of death	1 (reference)	1.09 (1.05, 1.15)	1.07 (1.04, 1.10)	1.15 (1.07, 1.24)
2 Major Chronic Disease				
Original model	1 (reference)	1.75 (1.62, 1.88)	1.23 (1.16, 1.31)	1.93 (1.68, 2.21)
Model considering competing risk of death	1 (reference)	1.75 (1.62, 1.89)	1.23 (1.16, 1.30)	1.93 (1.68, 2.20)

2. Could you clarify when the healthy lifestyle was collected? Was it measured at the same time as exposure at baseline?

[Response]

Yes, both lifestyle factors and exposure data were collected concurrently during baseline recruitment. We have revised the method section to clarify, **please see Page 7, line 154-155:** *"Healthy lifestyle score was created based on baseline information about 5 modifiable lifestyle factors[31-33], including smoking, body mass index, physical activity, diet and sleep hours.".*

3. In the Statistical analysis section, you mentioned "To investigate whether the loss of disease-free years due to loneliness or SI could be mitigated by adopting a healthy lifestyle". It sounds like healthy lifestyle is a mediator and you aimed to estimate the proportion of indirect effect among the total effect to me while you were estimating the interactive effect of loneliness/SI with healthy lifestyle. Could you rephrase it and throughout the paper to avoid confusion?

[Response]

We thank the reviewer for the comment! We have rephased the related sentence throughout the paper. For example, we have revised the aim in the Abstract to: "*We aimed to comprehensively assess the associations between loneliness and SI and life expectancy (LE) free from major physical and mental illness, in combination with healthy lifestyle levels.*" **Please see line 27-29.**

We have revised the aim in the introduction to: "*In this study, using data from UK biobank, we aimed to quantify the associations of loneliness and SI with LE free of major chronic diseases, including both major physical diseases (type 2 diabetes, cardiovascular disease, chronic respiratory disease, neurodegenerative disease and cancer) and mental diseases (depression and anxiety) in total population and among individuals with different levels of health lifestyle*.". **Please see line 69-73.**

4. Instead of combining lifestyle and exposure into a new variable, do you consider adding the product term between exposure and healthy lifestyle in your model to assess how the association would change in different levels of healthy lifestyle? This could also help quantify how the lifestyle would interact with exposure on the outcome and test the significance.

[Response]

Thanks for the comments. We fully agree with the Reviewer that it is important to assess how the association between exposure and life expectancy changes at different levels of healthy lifestyle. This is exactly the main purpose of our joint analysis of exposure and healthy lifestyle. But unfortunately, estimating the interaction terms in the model may not be appropriate because disease-free life expectancy is estimated by **integrating three sources** (prevalence, HR, and transition rate) **from three transitions in health status** (the three transitions include from non-disease to incident disease, from non-disease to death, and from disease diagnosis to death, as mentioned in comment 1). Moreover, since the current exposure grouping is a categorical variable (there is no obvious ordinal relationship within the group, such as association between social isolation and loneliness), the calculated interaction terms are difficult to interpret. **Thus, estimating the interaction terms of the three transitions separately may not adequately reflect the overall estimate of life expectancy.** Instead, we calculated the absolute estimates of life expectancy for each joint category and compared the difference in life expectancy in years directly. We believe that such analysis can meet the purpose of analysis (how the association between exposure and life expectancy changes in different levels of healthy lifestyle). In our previous study, we have performed similar analysis which aims to assess whether the association of cardiovascular health with life expectancy differed by socioeconomic status (*JAMA Intern Med. 2023 Apr 1;183(4):340-349.*).

Reviewer #4 (Remarks to the Author):

The study by Wang and colleagues examined the association between loneliness, social isolation, and LE free of physical and mental disease. They found loneliness and social isolation are more strongly associated with LE free of mental disease than with LE free of physical disease. Interestingly, they also found the loss of disease-free LE associated with social isolation narrowed with increasing levels of healthy lifestyle, but the loss of disease-free LE associated with loneliness did not. The novelty of the article is the inclusion of mental health in the calculation of disease-free life expectancy. This assessment of "aging" is very similar to the concept of "healthy aging", but it provides a more intuitive means of assessment. I have some comments that may improve the importance of this study.

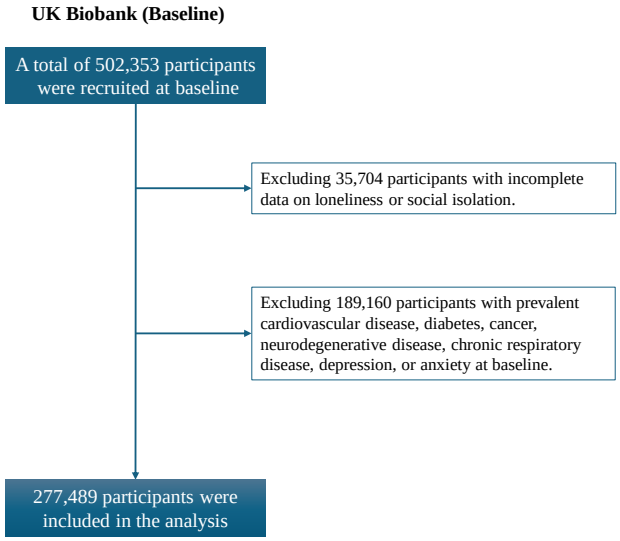
[Response]

We greatly appreciate the Reviewer's positive and useful comments, which were very helpful in improving the manuscript! We have carefully addressed all the comments and revised the manuscript accordingly.

1. The authors included a total of 277,489 participants from the UK Biobank. To allow for replication of the results, the manuscript would benefit from including a flow chart of sample selection.

[Response]

Thanks for the comment. As suggested, we have drawn a flow chart to describe the sample selection process, please see it in **Supplementary Figure 1** or below:



Supplementary Figure 1. The flow chat of sample selection.

2. To get a general idea of the follow-up length, please provide at least the median (IQR).

[Response]

Thanks for the comments. We have provided the median (IQR) duration of follow-up in the **Results** part. **Please see line 181-182:** "*During t a median (IQR) follow-up of 13.8 (1.4) and 13.4 (2.2) years, a total of 16,356 events of death and 78,829 events of 7 major chronic diseases were recorded, respectively.*"

3. How did authors deal with the missing data on covariates? Please declare the number or percentage for missing covariates.

[Response]

Thanks for the comments! Given the small amount of missing data (normally≤5% for a given covariate, *JAMA. 2020;323(12):1151-1160*), we coded missing data as a missing indicator category for categorical variables such as smoking status, and with mean values for continuous variables. Similar methods of dealing with missing values have been widely used in other studies (*JAMA. 2020;323(12):1151-1160; Eur Heart J. 2020 Mar 14;41(11):1182-1189.; JAMA Intern Med. 2020 Apr 1;180(4):513-523.*). We also noted this point in the method section, **please see line 141-142:** *"We coded missing covariates as a missing indicator category for categorical variables and with mean values for continuous variables."*

4. Table 1 summarized only the average minutes of physical activity across exposure groups. How about the percentage of low or high-risk lifestyle factors?

[Response]

Thanks for the comments. As suggested, we have added a Supplementary Table to show the percentage of low or high-risk lifestyle factors and revised the Results section to highlight. Please see **Supplementary Table 2** or below:

Supplementary Table 2. Baseline characteristics of low or high-risk lifestyle factors by combined categories of loneliness and SI status.

Characteristic	No loneliness or SI	Loneliness only	SI only	Loneliness and SI
Smoking, n (%)				
Non-current smoking	214208 (91.4)	7652 (87.9)	14860 (84.6)	1687 (81.5)
Current smoking	20063 (5.6)	1053 (12.1)	2702 (15.4)	384 (18.5)
Body Mass Index, n (%)				
Normal Boby Mass Index	84497 (36.1)	2828 (32.5)	6249 (35.6)	703 (33.9)
Abnormal Boby Mass Index	149774 (63.9)	5877 (67.5)	11313 (64.4)	1368 (66.1)
Physical activity, n (%)				
Regular physical activity	144466 (61.7)	5071 (58.3)	8465 (48.2)	955 (46.1)
Irregular physical activity	89805 (38.3)	3634 (41.8)	9097 (51.8)	1116 (53.9)
Diet, n (%)				
Healthy diet	159315 (68.0)	5320 (61.1)	11644 (66.3)	1206 (58.2)
Unhealthy diet	74956 (32.0)	3385 (38.9)	5918 (33.7)	865 (41.8)
Sleep, n (%)				
Sleep 7- < 9 hours	170670 (72.9)	5561 (63.9)	11637 (66.3)	1228 (59.3)
Sleep < 7 or ≥ 8 hours	63601 (27.2)	3144 (36.1)	5925 (33.7)	843 (40.7)

5. I wonder whether there is a significant interaction between social isolation and loneliness on life expectancy or on the risk of mortality

[Response]

Thanks for the comments. We estimated life expectancy using a multi-state life table, a method that does not directly assess interactions between social isolation and loneliness. In this study, we classified participants into 4 groups, participants without loneliness or SI, with loneliness only, with SI only, and with both loneliness and SI. This allowed us to estimate and compare life expectancy across groups and assess statistical significance. Following your suggestion, we have performed analysis to test interaction between social isolation and loneliness on the risk of mortality. We observed that the interaction between social isolation and loneliness was not significant, with *P* for interaction = 0.292.

Reviewer #1:

General Comments:

The study investigates an important and timely topic—how loneliness and social isolation (SI) affect life expectancy free of major chronic diseases and the potential mitigating effect of a healthy lifestyle. The UK Biobank cohort provides a large sample size, which is a major strength. However, there are several critical methodological, analytical, and interpretational concerns that need to be addressed to enhance the rigor and validity of the findings.

[Response]

We greatly appreciate the Reviewer's comments and suggestions, which are very insightful and useful, and we have carefully revised our manuscript accordingly. Please kindly find the point-by-point responses as follows.

Major Concerns:

1. Conceptual and Theoretical Framework

The manuscript does not adequately define the distinction between loneliness and social isolation beyond stating that loneliness is a subjective feeling while SI is an objective condition. However, there is a lack of discussion on how these constructs are interrelated and whether they could confound or interact with each other.

[Response]

Thanks for the comments! We have rephase the relative sentences to provide adequate details on the distinction between loneliness and social isolation. **Please see Page 4, line 27-30**: *"Notably, despite being related, loneliness and SI are distinct constructs, reflecting different aspects of social contact. SI is an objective measure of the quantity of social connection in behavior, while loneliness is a subjective measure of a person's emotional dissatisfaction with the quality of their relationships."*

Indeed, social isolation and loneliness are considered related; We share your concern and have factored this into our analysis. In the main analysis, we created the exposure by jointly considering both isolation and loneliness status, classifying participants into 4 groups: participants without loneliness or SI, with loneliness only,

with SI only, and with both loneliness and SI, which could partly solve this problem. Also, for your review, we performed an analysis to show the difference between HRs when only include loneliness or SI in the model and when loneliness and SI are mutually adjusted. We observed that the HRs were similar before and after mutual adjustment, suggesting that the potential interrelation may not have a material impact on our results. **Please see the Table below:**

	Model adjusted loneliness or SI only	Model mutual adjusted loneliness and SI
Loneliness	1.16 (1.13, 1.20)	1.15 (1.12, 1.19)
SI	1.09 (1.06, 1.17)	1.08 (1.05, 1.10)

The models were adjusted by age, race (Whites, Non-Whites), Townsend Deprivation Index (continuous), education levels (≤10 years, 11-19 years, and ≥20 years), and household income (<£18,000, £18,000–£29,999, £30,000–£51,999, £52,000–£100,000, and >£100,000).

The authors assume that a healthy lifestyle mitigates the effects of SI but not loneliness. This assumption is not well-justified theoretically, nor is there a mechanistic explanation provided.

[Response]

Thanks for the comments.

We did not assume that " *a healthy lifestyle can offset the lifespan damage caused by social isolation, but not the lifespan loss caused by loneliness.*" Our assumption in the introduction was " *Therefore, we assumed that a healthy lifestyle could partly alleviate or compensate for the loss of disease-free LE associated with loneliness or SI.*" (**line 45-47**). However, our results did not fully support my initial hypothesis (*Intriguingly, the loss of disease-free LE associated with SI substantially narrowed with increasing levels of healthy lifestyles in women and men, whereas the loss of disease-free LE associated with loneliness did not.* **Line 226-228**), and we also discussed this: *Partially consistent with the hypothesis of this study, we found that a healthy lifestyle appeared to alleviate the loss of disease-free LE associated with SI in both women and men, but not for the loss of disease-free LE associated with loneliness. Because the association between healthy lifestyle and longer disease-free life has been well established, our findings may reflect differences in the associations of loneliness and social isolation with health-related behaviors. Notably, previous findings that found significant associations between loneliness and health behaviors were mostly based on cross-sectional study design. A prospective study from England*

found that SI was associated with a range of health-related behaviors, but loneliness was not associated with health-related behaviors or BMI over a 10-year follow-up period in older English adults. Moreover, another study showed that there may be no mediator on the association between loneliness and the risk of depression. Taken together, our findings suggest that lifestyle behaviors may not play a role in the association between loneliness and adverse health outcomes, and other potential pathways, such as psychological stress and neuroinflammation, may be involved and need further exploration. Thus, lifestyle interventions may not be a priority option for participants with loneliness, whereas it may be a potential intervention for participants with SI, and future research is needed to validate our results. **Please see line 264-279 in the revised manuscript.**

2. Measurement Issues

Loneliness and Social Isolation Assessment: The study relies on a simplistic classification of loneliness and SI based on self-reported items from the UK Biobank. The psychometric properties (e.g., reliability and validity) of these measures are not discussed.

[Response]

We thank the reviewer for suggesting that loneliness and social isolation assessments rely on several simple questions and may not be able to adequately assess the complex phenomenon of social networking and interaction. However, these scales included in our study have been widely used in several previous studies from different cohorts (*Lancet Public Health. 2017 May 4;2(6):e260-e266.; Heart. 2018 Sep;104(18):1536-1542.; Lancet Public Health. 2023 Jan 17;S2468-2667(22)00253-5.; Lancet Public Health. 2021 Apr;6(4):e232-e239.)* and have been consistently related to various health outcomes, including CVD, dementia, hospital infection, and all-cause mortality, suggesting such scales are validated in capturing these variables in population studies. We acknowledge that more detailed measures of social networks may provide additional information and have discussed this issue in the revised manuscript. **Please see pages 15, line 285-289: "***First, loneliness and SI were assessed by a 2-item and 3-item scales, respectively, which may not be able to adequately assess the complex phenomenon of social networking and interaction. However, these measures have been widely used in previous studies from different cohorts*[22-24]*, suggesting such scales are effective in population studies. Multi-item assessment of loneliness or SI had better predictive validity than single-item*

measures.”.

Lifestyle Factors: The healthy lifestyle score is composed of smoking, BMI, physical activity, diet, and sleep duration. However, lifestyle is more complex than these five variables. For example, alcohol consumption and substance misuse are missing. The categorization into three groups (unhealthy, medium, and healthy) may oversimplify the nuances of lifestyle effects.

[Response]

Thanks for the comments! Indeed, a great number of studies, including our own, have found that moderate alcohol consumption is significantly negatively correlated with various diseases or death. However, in this study, we do not tend to include moderate alcohol consumption in the healthy lifestyle score, mainly based on the following two points. First, even moderate alcohol consumption is significantly positively correlated with the risk of some cancers, and the outcome of this study is healthy life expectancy free from various diseases. We need to consider a variety of diseases including cancer. Second, from the perspective of public recommendation, adding moderate alcohol consumption to the recommended elements of a healthy lifestyle will bring additional risks, especially among people who already have mild mental health problems. Moreover, substance misuse is important but beyond the scope of the current study and would be very interesting to explore next. Therefore, after referring to many previous studies, we decided not to include alcohol consumption in the healthy lifestyle score. (*Am J Prev Med. 2022. 63(1): 33; Cardiovasc Diabetol. 2021. 20: 1; CIRCULATION. 2022;146(5):e18-e43*).

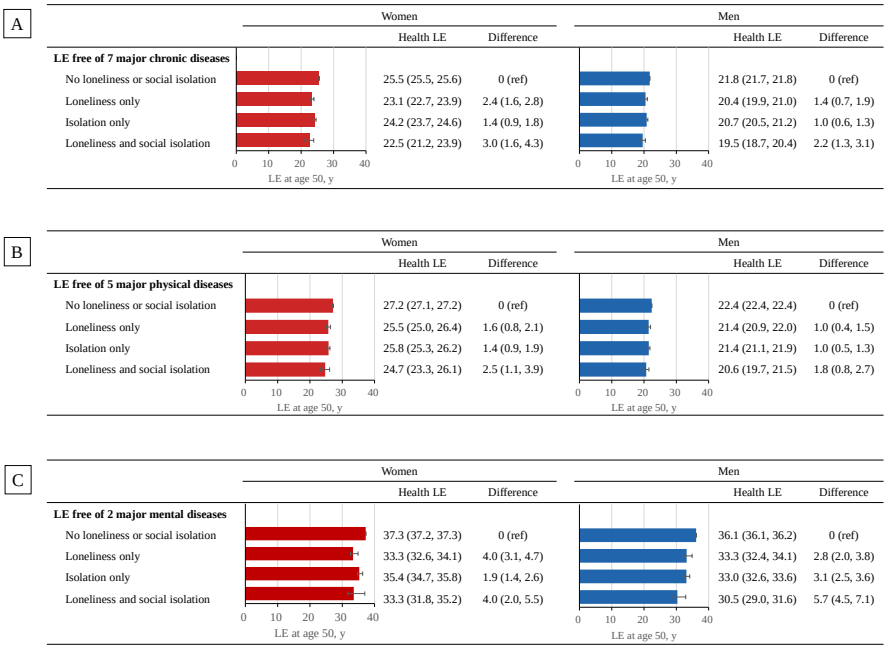
Regarding the grouping method for healthy lifestyles, we referred to a large number of previous references (*JAMA*. 2019 Aug 6;322(5):430-437; *N Engl J Med* 2016;375:2349-2358; *BMJ*. 2018 Nov 21:363:k4641.). The advantage of this simple classification method is that it is easy to promote to the general public. We also emphasized in the discussion that the lifestyle classification method used in this study is somewhat simplistic: “*The categorization into three groups (unhealthy, medium, and healthy) may also oversimplify the nuances of lifestyle effects.*” **Please see line 292-294.**

3. Study Design and Statistical Methods

Survivor Bias and Reverse Causation: The analysis is conducted on participants free of seven diseases at baseline. However, healthier individuals are more likely to participate in long-term studies, which introduces selection bias. Those who are socially isolated or lonely might already have underlying conditions that contribute to worse health outcomes. The authors should perform sensitivity analyses excluding participants with very short follow-up times.

[Response]

Thanks for the comments! Indeed, the reverse causality bias is a common issue in observational studies. It is also a routine practice to exclude participants with diseases at baseline to minimize the reverse causality bias in cohort studies (*Circulation. 2018 Jul 24;138(4):345-355; BMJ 2020;368:l6669*). As suggested, to minimize the impact of such potential bias, we performed a sensitivity analysis by excluding participants who became ill or died within two years, referring to solutions used in previous studies (*J Am Coll Cardiol. 2017 Mar, 69 (9) 1116–1125. BMJ 2019;365: l1628. Diabetes Care 2020;43(4):719–725. Diabetes Care 2020; 43: 2776–2784. Diabetes Care 2021; 44: 1–8*). The results from the sensitivity analysis remained similar to those from the main analysis. **Please see Supplementary Figure 2 or below**:



Supplementary Figure 2. The Estimated Life Expectancy Free of Chronic Diseases According to the Combined Categories of Loneliness and Social Isolation at Age 50 Years, excluding participants who became ill or died within two years

Statistical Models:

The multistate life table approach is appropriate, but the use of Gompertz distribution for transition probabilities should be justified. Alternative parametric models (e.g., Weibull) could be tested.

The method used to estimate life expectancy differences (Monte Carlo simulation) is appropriate, but more details on the number of iterations and convergence diagnostics should be reported.

[Response]

Thanks for the comments. For the estimation of life expectancy, the life table method using the Gompertz distribution is reliable and has been well recognized in previous studies (*JAMA Intern Med. 2023 Apr 1;183(4):340-349; Arch Intern Med. 2007 Jun 11;167(11):1145-51; BMJ 2020;368:l6669*). It is the established standard for calculating life expectancy, ensuring consistency and credibility, and ensuring that results across different studies are comparable. Methodologically, there are several reasons to choose Gompertz rather than Weibull distribution: 1) Gompertz more accurately describes the observed pattern of human mortality after early adulthood. Decades of data across countless populations consistently show that the Gompertz plot is linear over the critical age range that determines life expectancy. The Weibull plot does not fit as well. Gompertz is an observed empirical law for human senescence. 2) The parameters of the Gompertz model have a more intuitive and meaningful biological interpretation in the context of human aging. They directly describe the process of senescence. 3) Gompertz is more suitable for this study estimating the life expectancy between 50 to 100 years, since it provides more realistic extrapolations to the highest ages.

To estimate the confidence intervals of life expectancy, we used Monte Carlo simulation with 2000 iterations. We chose this number by following previous studies, and the Monte Carlo Standard Error (diagnostics indicator) was <0.1, indicating the simulation has reached an acceptable level of convergence for this study.

4. Interpretation of Findings

The authors claim that a healthy lifestyle mitigates the adverse effects of SI but not loneliness. However, this interpretation is problematic. It is possible that loneliness operates through different pathways (e.g., psychological stress, neuroinflammation)

rather than behavioural mechanisms, but this is not tested directly.

[Response]

Thanks for the constructed suggestions! We have revised the discussion to further discuss the potential pathways that underlying the association between loneliness and adverse health outcomes. **Please see page 15, line 274-279:** "*Taken together, our findings suggest that lifestyle behaviors may not play a role in the association between loneliness and adverse health outcomes, and other potential pathways, such as psychological stress and neuroinflammation, may be involved and need further exploration. Thus, lifestyle interventions may not be a priority option for participants with loneliness, whereas it may be a potential intervention for participants with SI, and future research is needed to validate our results.*"

The magnitude of effect sizes, particularly for mental health outcomes, is substantial. The loss of 3.9 years of life expectancy free of mental diseases for lonely women is striking. The authors should clarify whether these estimates are robust across sensitivity analyses.

[Response]

Thanks for the comments. As suggested, we performed a sensitivity analysis by excluding participants who became ill or died within two years. The results from the sensitivity analysis remained similar to those from the main analysis. **Please see Supplementary Figure 2 or above**. Also, we have revised the manuscript to further discuss the results that women tended to have a greater impact of loneliness, **please see Page 14, line 253-258: "***In addition, we observed that for the LE free of mental disease, women tended to have a greater impact of loneliness, but man seemed to experience a greater impact of SI. One potential explanation for these findings might be the sex-based differences in social needs and their distinct connections to health. Men and women may follow differential pathways to obtain support and achieve psychological well-being, with men tending to require more objective support and women more emotional support.***"**

The study does not address potential sex differences in the effects of loneliness and SI. Although separate estimates are presented for men and women, no discussion is

provided on why men seem to experience a greater impact of SI on mental health outcomes.

[Response]

Thanks for the useful suggestion! Because age-specific mortality rate differed between women and men, we performed analysis to separately estimate the SI and loneliness related LE for women and men. It may not appropriate to directly compare the results of men and women, however, we try our best to seek some clues to potentially explain these results. As you mentioned (**Figure 1C**), we observed that for the LE free of mental disease, women tended to have a greater impact of loneliness, but man seemed to experience a greater impact of SI. The sex-based differences in social needs and their distinct connections to health could partly explain these results. There may be differences in the ways men and women obtain support and achieve psychological well-being. Rather than men are more fragile or women are more sensitive, the core issue is the matching of social needs. Men tend to need more objective support, while women need more emotional support, resulting in corresponding different impacts on health. We have revised the Results and Discussion to provide more details, **please see Page 14, line 253-258: "***In addition, we observed that for the LE free of mental disease, women tended to have a greater impact of loneliness, but man seemed to experience a greater impact of SI. One potential explanation for these findings might be the sex-based differences in social needs and their distinct connections to health. Men and women may follow differential pathways to obtain support and achieve psychological well-being, with men tending to require more objective support and women more emotional support.***"**

Minor Concerns:

Terminology: The phrase "healthy lifestyle mitigates the impact of SI" may be misleading. A more accurate phrasing would be "healthy lifestyle is associated with a reduced impact of SI."

[Response]

Thanks for the comments. We have revised the relative sentence to clarify. **Please see page 8, line 128-130**: *"To investigate whether the loss of disease-free years due to loneliness or SI would reduce with increasing levels of healthy lifestyle, we investigated joint associations of healthy lifestyle score with loneliness and SI status in relation to life expectancy free of diseases."*

Figures and Tables: Some figures (e.g., Figures 3 and 4) are difficult to interpret due to overlapping confidence intervals. Improved visualisation techniques (e.g., stratified plots) should be considered.

[Response]

As suggested, we have changed the visualization to show the stratified plots. Please see revised **Supplementary Figure 4** and **Supplementary Figure 5** in the submitted documents or below. Also, we have changed the original Figure 3 and Figure 4 to Table 2 and Table 3, respectively, to show details.

Healthy Lifestyles	Women			Men		
	Non-loneliness	*Loneliness*	*Difference*	*Non-loneliness*	*Loneliness*	*Difference*
LE free of 7 major chronic diseases						
Unhealthy (0-2 favorable factors)	22.8 (22.6, 23.0)	20.4 (19.4, 21.3)		19.8 (19.6, 20.0)	19.0 (18.2, 19.7)	
Medium (3 favorable factors)	24.9 (24.7, 25.1)	24.1 (23.1, 25.1)		21.6 (21.4, 21.7)	20.7 (19.9, 21.6)	
Healthy (4-5 favorable factors)	26.9 (26.8, 27.1)	24.7 (23.8, 25.7)		23.3 (23.1, 23.4)	22.1 (21.1, 23.1)	
LE free of 5 major physical diseases						
Unhealthy (0-2 favorable factors)	24.4 (24.1, 24.6)	23.1 (22.0, 24.1)		20.4 (20.3, 20.6)	19.5 (18.9, 20.0)	
Medium (3 favorable factors)	26.5 (26.3, 26.7)	26.7 (25.6, 27.8)		22.2 (22.0, 22.3)	22.2 (21.5, 22.8)	
Healthy (4-5 favorable factors)	28.5 (28.4, 28.7)	26.7 (25.7, 27.7)		23.9 (23.7, 24.0)	23.6 (22.8, 24.3)	
LE free of 2 major mental diseases						
Unhealthy (0-2 favorable factors)	34.8 (34.4, 35.1)	31.6 (30.2, 32.9)		33.3 (33.0, 33.6)	30.7 (29.5, 31.8)	
Medium (3 favorable factors)	36.7 (36.5, 36.9)	34.1 (32.8, 35.4)		35.9 (35.8, 36.1)	33.7 (32.7, 34.7)	
Healthy (4-5 favorable factors)	38.3 (38.1, 38.5)	34.1 (32.9, 35.3)		38.0 (37.6, 38.3)	36.8 (34.3, 39.0)	

Supplementary Figure 4. Association of Loneliness and Healthy Lifestyle with Estimated Life Expectancy Free of Chronic Diseases at Age 50 Years.

Healthy Lifestyles	Women			Men		
	Non-social isolated	*Social isolated*	*Difference*	*Non-social isolated*	*Social isolated*	*Difference*
LE free of 7 major chronic diseases						
Unhealthy (0-2 favorable factors)	22.9 (22.6, 23.1)	20.9 (20.2, 21.6)		19.9 (19.7, 20.0)	18.8 (18.3, 19.3)	
Medium (3 favorable factors)	24.9 (24.7, 25.1)	23.9 (23.1, 24.6)		21.5 (21.4, 21.7)	21.4 (20.8, 22.0)	
Healthy (4-5 favorable factors)	26.8 (26.7, 27.0)	27.2 (26.4, 28.0)		23.2 (23.1, 23.4)	23.0 (22.2, 23.6)	
LE free of 5 major physical diseases						
Unhealthy (0-2 favorable factors)	24.5 (24.3, 24.8)	22.4 (21.6, 23.1)		20.5 (20.3, 20.7)	19.5 (18.9, 20.0)	
Medium (3 favorable factors)	26.6 (26.4, 26.8)	25.5 (24.8, 26.3)		22.1 (22.0, 22.3)	22.2 (21.5, 22.8)	
Healthy (4-5 favorable factors)	28.4 (28.3, 28.6)	28.8 (27.9, 29.6)		23.9 (23.7, 24.0)	23.6 (22.8, 24.3)	
LE free of 2 major mental diseases						
Unhealthy (0-2 favorable factors)	34.9 (34.5, 35.2)	32.6 (31.6, 33.6)		33.9 (33.7, 34.2)	31.2 (30.4, 31.9)	
Medium (3 favorable factors)	36.7 (36.4, 36.9)	35.6 (34.6, 36.5)		35.8 (35.6, 36.1)	33.6 (32.7, 34.5)	
Healthy (4-5 favorable factors)	38.2 (38.0, 38.3)	37.6 (36.6, 38.5)		37.2 (37.0, 37.4)	35.3 (34.2, 36.2)	

Supplementary Figure 5. Association of Social Isolation and Healthy Lifestyle with Estimated Life Expectancy Free of Chronic Diseases at Age 50 Years

Causal Language: The study is observational, yet some statements imply causation (e.g., “adopting a healthy lifestyle may substantially offset disease-free LE losses”). The authors should be more cautious in phrasing conclusions.

[Response]

Thanks for the comments. We have revised the relative statement. **Please see page 14, line 264-266**: *“Partially consistent with the hypothesis of this study, we found that a healthy lifestyle appeared to alleviate the loss of disease-free LE associated with SI in both women and men, but not for the loss of disease-free LE associated with loneliness.”* and **page 16, line 301-302**: *“A healthy lifestyle may alleviate the loss of disease-free LE due to SI but does not appear to alleviate the loss of disease-free LE due to loneliness.”*.

Reviewer #3:

The authors did a great job on estimating the joint association of loneliness and social isolation with chronic-disease free life expectancy using data from UK biobank by sex. They also assessed if the association differs by healthy lifestyle factors. They found that loneliness and social isolation are associated with shorter life expectancy and lifestyle factor interacted with social loneliness.

[Response]

We greatly appreciate the Reviewer's encouraging and constructive comments. The Reviewer's comments and suggestions are very insightful and useful, and we have carefully revised our manuscript accordingly. Please kindly find the point-by-point responses as follows.

1. Was the death information used in the analysis all-cause death or death caused by the 7 chronic diseases of interest? If it was all-cause death, would it introduce some bias when calculating disease free life expectancy? Would the competing risk overestimate the life expectancy you estimated?

[Response]

Thank you very much for your valuable comments! In multistate lifetable method, only all-cause mortality is utilized to estimate disease-free life expectancy. A competing risk arises when individuals are at risk of multiple events, and the occurrence of one event (death) can prevent the occurrence of others (disease). If our analysis considers only **Transition 1 (from non-disease to incident disease)**, competing risks could be accounted for. However, multistate lifetable needs to consider 3 transitions simultaneously (**Transition 2: from non-disease to death; Transition 3: from disease diagnosis to death, please see Figure below**). **If we further accounted for the competing risk of death in Transition 1, the information on death would have been considered repeatedly, which is already included in transition 2.** Thus, we think it may not be appropriate to re-consider the competing risk of death in transition 1 when calculating the disease-free life expectancy using multistate lifetable method. The multistate lifetable method used in this study has been widely used in previous studies and is well-established within the academic community (*JAMA Intern Med. 2023 Apr 1;183(4):340-349.; BMJ. 2020*

Jan 8:368:l6669.; Arch Intern Med. 2007 Jun 11;167(11):1145-51.).

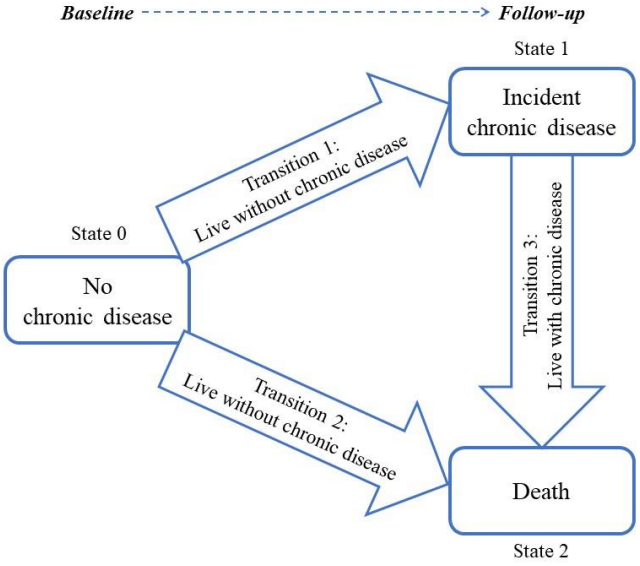


Diagram 1, Schematic diagram for three transitions over the time of follow-up.

In addition, as your suggestions, we performed the analysis to consider the competing risk of death in Transition 1. We observed that the results were very similar before and after accounting for competing risk of death. Please see the Table below:

Table. HR for transition 1 before and after considering competing risk of death

Model	HR (95% CI)			
	No loneliness or SI	Loneliness only	SI only	Loneliness and SI
7 Major Chronic Disease				
Original model	1 (reference)	1.16 (1.12, 1.20)	1.08 (1.05, 1.11)	1.22 (1.14, 1.31)
Model considering competing risk of death	1 (reference)	1.16 (1.12, 1.20)	1.08 (1.05, 1.11)	1.22 (1.14, 1.31)
5 Major Chronic Disease				
Original model	1 (reference)	1.09 (1.05, 1.14)	1.07 (1.04, 1.10)	1.15 (1.07, 1.24)
Model considering competing risk of death	1 (reference)	1.09 (1.05, 1.15)	1.07 (1.04, 1.10)	1.15 (1.07, 1.24)
2 Major Chronic Disease				
Original model	1 (reference)	1.75 (1.62, 1.88)	1.23 (1.16, 1.31)	1.93 (1.68, 2.21)
Model considering competing risk of death	1 (reference)	1.75 (1.62, 1.89)	1.23 (1.16, 1.30)	1.93 (1.68, 2.20)

2. Could you clarify when the healthy lifestyle was collected? Was it measured at the same time as exposure at baseline?

[Response]

Yes, both lifestyle factors and exposure data were collected concurrently during baseline recruitment. We have revised the method section to clarify, **please see Page 8, line 134-136:** *"Healthy lifestyle score was created based on baseline information about 5 modifiable lifestyle factors[31-33], including smoking, body mass index, physical activity, diet and sleep hours.".*

3. In the Statistical analysis section, you mentioned "To investigate whether the loss of disease-free years due to loneliness or SI could be mitigated by adopting a healthy lifestyle". It sounds like healthy lifestyle is a mediator and you aimed to estimate the proportion of indirect effect among the total effect to me while you were estimating the interactive effect of loneliness/SI with healthy lifestyle. Could you rephrase it and throughout the paper to avoid confusion?

[Response]

We thank the reviewer for the comment! We have rephased the related sentence throughout the paper. For example, we have revised the aim in the Abstract to: "*We aimed to evaluate the association between loneliness, SI and life expectancy (LE) free of major physical and mental diseases and estimate the extent to which a healthy lifestyle compensates for the loss of disease-free years related to loneliness or SI, respectively.*" **Please see line 3-6.**

We have revised the aim in the introduction to: "*In this study, we aimed to quantify the associations of loneliness and SI with LE free of major chronic diseases, including both major physical diseases (type 2 diabetes, cardiovascular disease, chronic respiratory disease, neurodegenerative disease and cancer) and mental diseases (depression and anxiety) in adults from the UK Biobank. Furthermore, we quantified the extent to which a healthy lifestyle compensates for the loneliness- or SI-related loss of disease-free years.*". **Please see line 48-52.**

4. Instead of combining lifestyle and exposure into a new variable, do you consider adding the product term between exposure and healthy lifestyle in your model to assess how the association would change in different levels of healthy lifestyle? This could also help quantify how the lifestyle would interact with exposure on the outcome and test the significance.

[Response]

Thanks for the comments. We fully agree with the Reviewer that it is important to assess how the association between exposure and life expectancy changes at different levels of healthy lifestyle. This is exactly the main purpose of our joint analysis of exposure and healthy lifestyle. But unfortunately, estimating the interaction terms in the model may not be appropriate because disease-free life expectancy is estimated by **integrating three sources** (prevalence, HR, and transition rate) **from three transitions in health status** (the three transitions include from non-disease to incident disease, from non-disease to death, and from disease diagnosis to death, as mentioned in comment 1). Moreover, since the current exposure grouping is a categorical variable (there is no obvious ordinal relationship within the group, such as association between social isolation and loneliness), the calculated interaction terms are difficult to interpret. **Thus, estimating the interaction terms of the three transitions separately may not adequately reflect the overall estimate of life expectancy.** Instead, we calculated the absolute estimates of life expectancy for each joint category and compared the difference in life expectancy in years directly. We believe that such analysis can meet the purpose of analysis (how the association between exposure and life expectancy changes in different levels of healthy lifestyle). In our previous study, we have performed similar analysis which aims to assess whether the association of cardiovascular health with life expectancy differed by socioeconomic status (*JAMA Intern Med. 2023 Apr 1;183(4):340-349.*).

Reviewer #4:

The study by Wang and colleagues examined the association between loneliness, social isolation, and LE free of physical and mental disease. They found loneliness and social isolation are more strongly associated with LE free of mental disease than with LE free of physical disease. Interestingly, they also found the loss of disease-free LE associated with social isolation narrowed with increasing levels of healthy lifestyle, but the loss of disease-free LE associated with loneliness did not. The novelty of the article is the inclusion of mental health in the calculation of disease-free life expectancy. This assessment of "aging" is very similar to the concept of "healthy aging", but it provides a more intuitive means of assessment. I have some comments that may improve the importance of this study.

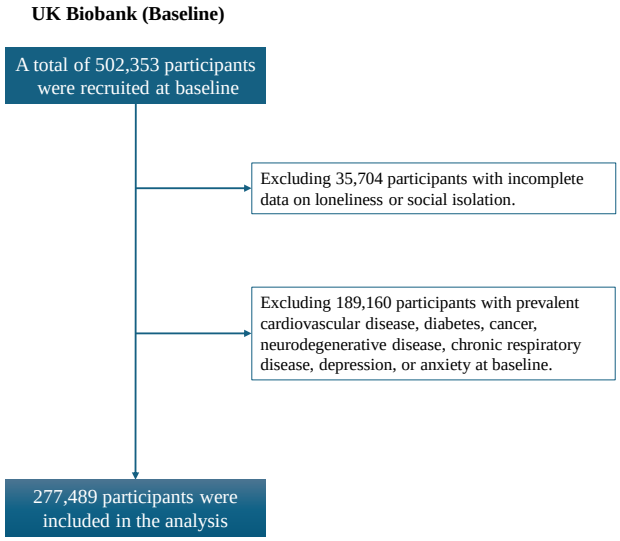
[Response]

We greatly appreciate the Reviewer's comments, which were very helpful in improving the manuscript! We have carefully addressed all the comments and revised the manuscript accordingly.

1. The authors included a total of 277,489 participants from the UK Biobank. To allow for replication of the results, the manuscript would benefit from including a flow chart of sample selection.

[Response]

Thanks for the comment. As suggested, we have drawn a flow chart to describe the sample selection process, please see it in **Supplementary Figure 1** or below:



Supplementary Figure 1. The flow chat of sample selection.

2. To get a general idea of the follow-up length, please provide at least the median (IQR).

[Response]

Thanks for the comments. We have provided the median (IQR) duration of follow-up in the **Results** part. **Please see line 161-162:** "*During t a median (IQR) follow-up of 13.8 (1.4) and 13.4 (2.2) years, a total of 16,356 events of death and 78,829 events of 7 major chronic diseases were recorded, respectively.*"

3. How did authors deal with the missing data on covariates? Please declare the number or percentage for missing covariates.

[Response]

Thanks for the comments! Given the small amount of missing data (normally≤5% for a given covariate, *JAMA. 2020;323(12):1151-1160*), we coded missing data as a missing indicator category for categorical variables such as smoking status, and with mean values for continuous variables. Similar methods of dealing with missing values have been widely used in other studies (*JAMA. 2020;323(12):1151-1160; Eur Heart J. 2020 Mar 14;41(11):1182-1189.; JAMA Intern Med. 2020 Apr 1;180(4):513-523.*). We also noted this point in the method section, **please see line 120-121:** *"We coded missing covariates as a missing indicator category for categorical variables and with mean values for continuous variables."*

4. Table 1 summarized only the average minutes of physical activity across exposure groups. How about the percentage of low or high-risk lifestyle factors?

[Response]

Thanks for the comments. As suggested, we have added a Supplementary Table to show the percentage of low or high-risk lifestyle factors and revised the Results section to highlight. Please see **Supplementary Table 2** or below:

Supplementary Table 2. Baseline characteristics of low or high-risk lifestyle factors by combined categories of loneliness and SI status.

Characteristic	No loneliness or SI	Loneliness only	SI only	Loneliness and SI
Smoking, n (%)				
Non-current smoking	214208 (91.4)	7652 (87.9)	14860 (84.6)	1687 (81.5)
Current smoking	20063 (5.6)	1053 (12.1)	2702 (15.4)	384 (18.5)
Body Mass Index, n (%)				
Normal Boby Mass Index	84497 (36.1)	2828 (32.5)	6249 (35.6)	703 (33.9)
Abnormal Boby Mass Index	149774 (63.9)	5877 (67.5)	11313 (64.4)	1368 (66.1)
Physical activity, n (%)				
Regular physical activity	144466 (61.7)	5071 (58.3)	8465 (48.2)	955 (46.1)
Irregular physical activity	89805 (38.3)	3634 (41.8)	9097 (51.8)	1116 (53.9)
Diet, n (%)				
Healthy diet	159315 (68.0)	5320 (61.1)	11644 (66.3)	1206 (58.2)
Unhealthy diet	74956 (32.0)	3385 (38.9)	5918 (33.7)	865 (41.8)
Sleep, n (%)				
Sleep 7- < 9 hours	170670 (72.9)	5561 (63.9)	11637 (66.3)	1228 (59.3)
Sleep < 7 or ≥ 8 hours	63601 (27.2)	3144 (36.1)	5925 (33.7)	843 (40.7)

5. I wonder whether there is a significant interaction between social isolation and loneliness on life expectancy or on the risk of mortality

[Response]

Thanks for the comments. We estimated life expectancy using a multi-state life table, a method that does not directly assess interactions between social isolation and loneliness. In this study, we classified participants into 4 groups, participants without loneliness or SI, with loneliness only, with SI only, and with both loneliness and SI. This allowed us to estimate and compare life expectancy across groups and assess statistical significance. Following your suggestion, we have performed analysis to test interaction between social isolation and loneliness on the risk of mortality. We observed that the interaction between social isolation and loneliness was not significant, with *P* for interaction = 0.292.

Reviewer #4:

The authors have addressed the previous comments well and have notably strengthened the manuscript. The clarity of the analyses and presentation has improved. Nevertheless, I have several comments that I believe would further strengthen the manuscript.

[Response]

We greatly appreciate the Reviewer's comments, which help a lot in improving the manuscript. We have further carefully revised the manuscript point-by-point. Please kindly find the responses as follows.

The "Multistate Life Table" approach relies on the Markov assumption (the future state depends only on the current state, not the history). Was this assumption tested? Please briefly mention how you addressed or validated this (e.g., by testing for time-dependent effects of loneliness/SI in the Cox models used to generate transition hazards). If not tested, this should be noted as a potential limitation.

[Response]

Thank you for this insightful observation. We fully agree that formally testing the Markov assumption is an important methodological consideration. Consistent with previous studies that calculated life expectancy using the multi-state life table method (*BMJ 2020;368:l6669*; *BMJ 2022;377:e068390; Arch Intern Med. 2007;167:1145-1151; Circulation. 2018;138:345–355.*), the Markov assumption is usually directly postulated rather than rigorously tested.

Many thanks to the reviewers for the comment on using time-dependent analysis to verify the assumption! Unfortunately, due to the lack of complete information on exposure factors (loneliness/SI) during the follow-up period in the UK Biobank (only a small number of participants having taken part in the surveys conducted during follow-up), we were unable to employ time-dependent analysis to verify the Markov assumption in this study. As suggested, we have added it as an important limitation, **please see line 299-303**: *"Third, although the method of calculating disease-free life expectancy using multi-state life table has been widely used in previous studies, it must be acknowledged that this method has limitations— the inherited Markov assumption has not been formally tested."*.

However, it should be noted that in the process of calculating the transition rates, this study did not include participants with prevalent diseases at baseline. Instead, it

considered three transition processes: from baseline health to incident disease during follow-up, from incident disease during follow-up to death, and from baseline health to death. Therefore, in this study, the possibility that the Markov assumption is violated due to the duration of illness is low, but we cannot rule out the possibility of its violation due to other factors.

For the joint analysis of loneliness/SI and lifestyle, the sample size in some strata (e.g., "lonely + healthy lifestyle") might be small, potentially affecting the precision of the life expectancy estimates. Please provide the number of participants in each joint category (e.g., in a supplementary table) to reassure readers about the stability of these estimates.

[Response]

Thanks for the suggestions! We have added a supplementary Table to show the number of participants in each joint category, please see **Supplementary Table 2 or below.**

Supplementary Table 2. Sample size for the joint categories of loneliness or social isolation status and levels of healthy lifestyle.

Healthy Lifestyles	**Women**		**Men**	
	Non-loneliness	***Loneliness***	***Non-loneliness***	***Loneliness***
Unhealthy (0-2 favorable factors)	32032	2012	24318	1430
Medium (3 favorable factors)	39291	1713	41351	1769
Healthy (4-5 favorable factors)	41597	1420	67100	2153
	Non-social isolated	***Social isolated***	***Non-social isolated***	***Social isolated***
Unhealthy (0-2 favorable factors)	30531	3513	23070	2678
Medium (3 favorable factors)	37865	3139	39787	3333
Healthy (4-5 favorable factors)	40154	2863	65679	3574

A major limitation is the use of baseline-only assessments for loneliness, SI, and lifestyle. These factors are dynamic and likely change over a follow-up period of 13 years. Please emphasize this more strongly in the limitations section, as it may lead to non-differential misclassification and an underestimation of the true associations. Additionally, could the online follow-up questionnaires provided by UK Biobank help address this issue?

[Response]

Many thanks for your comments! The UK Biobank did collect repeated measurements of loneliness and SI in subsequent online follow-up questionnaires among a small subset of participants, but the sample size would be too small if we were to incorporate these measurements into our analysis. Therefore, consistent with the majority of studies based on the UK Biobank (*Lancet Public Health. 2017 May 4;2(6):e260-e266.; Lancet Public Health. 2023 Feb;8(2):e109-e118.; Nat Hum Behav. 2024 Nov;8(11):2209-2221.*), the present study only used baseline exposure information. We have revised the manuscript to emphasize this point, **please see line 291-299**: *"Second, because only the baseline measurement of SI and loneliness was used in this study, we were unable to analyze the association of dynamic changes in these factors with disease-free LE, which may lead to non-differential misclassification and an underestimation of the true associations. There are few studies on the stability of social isolation or loneliness. A previous meta-analysis suggested that the trajectory of loneliness among middle-aged and older adults remains relatively stable, indicating that a single measurement of loneliness could serve as a valid indicator of long-term exposure [43]. A recent study found that nearly 50% of the participants experienced changes in their social isolation scores during a 4-year follow-up period [44]."*

The sentence regarding sensitivity analysis ("excluding participants who became ill or died within two years") is clear. However, please explicitly state the rationale for choosing a 2-year landmark period.

[Response]

We choose two years as the landmark period because of three reasons: first, based on the previous evidence (*Circ Cardiovasc Qual Outcomes. 2011 May;4(3):363-71.; J Womens Health. 1997 Feb;6(1):49-62.; Modern Epidemiology, 4th edition)*, two years is long enough to capture a high proportion of participants whose early disease onset is likely due to reverse causation. Second, two years is short enough to avoid excluding an excessive number of incident cases, which would undermine the study's statistical power and precision. Third, two years that align with common follow-up cycles in famous large cohort studies (often 2-4 years like Framingham heart study and Nurse Health Study), making it a practical and consistent choice for analysis. We have integrated this description into manuscript, **please see line 127-129**: *"We chose the two-year landmark period because it effectively balances bias reduction from*

reverse causation, preservation of statistical power, and alignment with common cohort study follow-up cycles."

REVIEWERS' COMMENTS

Reviewer #4 (Remarks to the Author):

No further comments.