Associations of face-to-face and non-face-to-face social isolation with all-cause and cause-specific mortality: 13-year follow-up of the Guangzhou Biobank Cohort study

Jiao Wang1, Wei Sen Zhang2*, Chao Qiang Jiang2, Feng Zhu2, Ya Li Jin2, Kar Keung Cheng3, Tai Hing Lam4 and Lin Xu1,4*

Abstract
Background: Although social isolation has been associated with a higher mortality risk, little is known about the potential different impacts of face-to-face and non-face-to-face isolation on mortality. We examined the prospective associations of four types of social isolation, including face-to-face isolation with co-inhabitants and non-co-inhabitants, non-face-to-face isolation, and club/organization isolation, with all-cause and cause-specific mortality separately.

Methods: This prospective cohort study included 30,430 adults in Guangzhou Biobank Cohort Study (GBCS), who were recruited during 2003–2008 and followed up till Dec 2019.

Results: During an average of 13.2 years of follow-up, 4933 deaths occurred during 396,466 person-years. Participants who lived alone had higher risks of all-cause (adjusted hazard ratio (AHR) 1.24; 95% confidence interval (CI) 1.04–1.49) and cardiovascular disease (CVD) (1.61; 1.20–2.03) mortality than those who had ≥ 3 co-habitant contact after adjustment for thirteen potential confounders. Compared with those who had ≥ 1 time/month non-co-inhabitant contact, those without such contact had higher risks of all-cause (1.60; 1.20–2.00) and CVD (1.91; 1.20–2.62) mortality. The corresponding AHR (95% CI) in participants without telephone/mail contact were 1.27 (1.14–1.42) for all-cause, 1.30 (1.08–1.56) for CVD, and 1.37 (1.12–1.67) for other-cause mortality. However, no association of club/organization contact with the above mortality and no association of all four types of isolation with cancer mortality were found.

Conclusions: In this cohort study, face-to-face and non-face-to-face isolation were both positively associated with all-cause, CVD-, and other-cause (but not cancer) mortality. Our finding suggests a need to promote non-face-to-face contact among middle-aged and older adults.

Keywords: Social isolation, Face-to-face contact, Non-face-to-face contact, Mortality, Cardiovascular disease

Background
Social isolation is defined as “a state in which the individual lacks a sense of belonging socially, lacks engagement with others, has a minimal number of social contact and they are deficient in fulfilling and quality relationships” [1, 2]. It has been shown to be associated with higher risks of heart disease and stroke [3], dementia [4], and mortality [5]. Though the adverse effect on mortality was...
comparable to or greater than some well-established risk factors [6, 7], it has received less attention [8]. Social isolation is a growing epidemic in older people. For example, the prevalence is 24% in the USA [9], 10–43% in North America [2], 20% in India [10], and 33.1% in China [11]. During the coronavirus disease (COVID)-19 pandemic, “social distancing” measures have aggravated pre-existing social isolation [12]. The American Association of Retired Persons reported that 14% of adults aged 50+ years in the USA were socially isolated in 2017, and the percentage reached 61% in 2020 since the pandemic began [12], when face-to-face contact is heavily restricted, and non-face-to-face contact (i.e., conventionally by telephone and letter, or recently by e-mail and social media) become the predominant forms of social interactions. However, the associations of face-to-face and non-face-to-face contact with mortality have not been well-defined and differentiated in previous studies.

A meta-analysis of 70 prospective studies published up to 2014 reported 29% higher risk of mortality associated with social isolation and loneliness [13], and another meta-analysis of 91 studies up to 2015 reported 13% higher risk of mortality associated with lower levels of social contact frequency [14]. But no study in the two meta-analysis papers above reported face-to-face and non-face-to-face contact separately. We found thirty studies published after these two meta-analyses (Additional file 1: Table S1) [5, 15–43]. Of them, only one study (n = 1023) classified participants according to social isolation types (face-to-face and non-face-to-face) [30]. However, this study only reported the all-cause (no CVD and cancer) mortality risk related to the co-existence of social (non-face-to-face) isolation and homebound status but did not report results of non-face-to-face contact separately [30]. In the context of physiological mechanisms, a previous study showed that only in-person contacts, but not virtual contact, protected against mood disorders [44], which indicated non-face-to-face contacts might have a different effect on human health, even though face-to-face contacts have been repeatedly linked to better health outcomes [5, 32].

We investigated the prospective associations of face-to-face and non-face-to-face social isolation with all-cause and cause-specific mortality in 30,430 participants who were recruited in 2003–2008 and had all-cause and cause-specific mortality follow-up data up to December 2019 in the Guangzhou Biobank Cohort Study (GBCS).

**Methods**

**Study participants**

The Guangzhou Biobank Cohort Study (GBCS) in China is a 3-way collaborative project among the Guangzhou Twelfth People’s Hospital and the Universities of Hong Kong and Birmingham. Participants were recruited from a community social and welfare association, the “Guangzhou Health and Happiness Association for the Respectable Elders” (GHHARE). From 2003 to 2008, 32,850 members of the GHHARE were invited, and of them, 30,430 agreed to participate and signed informed consents, with a response rate of 92.6%. GHHARE is a large unofficial organization with ten branches throughout all districts of Guangzhou. Membership of this association is open to Guangzhou residents aged 50 years or older for a nominal, monthly fee of 4 Chinese yuan renminbi (CNY) (about 50 US cents). Seven percent of local residents aged 50+ years enrolled in the GHHARE. All surviving participants were invited to return for follow-up examination from March 2008 to December 2012. Details of the GBCS, GHHARE, and some prospective study results have been reported previously [45–47]. Briefly, baseline information was collected using a computer-based questionnaire in face-to-face interviews by trained nurses in the Guangzhou Twelfth People’s Hospital. Information of demographic characteristics, lifestyle factors, family and personal medical history, and anthropometrics, blood pressure, fasting plasma glucose, lipids, and inflammatory markers was collected following standard protocols. The reliability and validity of the questionnaire were tested 6 months into recruitment by recalling 200 randomly selected participants for re-interview, and the results were satisfactory [45].

**Social isolation measurement**

Since no study has reported face-to-face and non-face-to-face contact separately, we first proposed the 4 types of social contact using the validated questions in the Berkman-Syme Social Network Index (SNI) [48] with appropriate revise. The four types of social contact were illustrated in Fig. 1 and described in Table 1. We included mail as another way of non-face-to-face contact besides telephone, since the telephone and mail are the commonest non-face-to-face ways to contact others in 2003, before smartphone, Internet, and social media had become popular. A composite social isolation score was derived from the sum of four types of social isolation, with a score from 0 to 7. A higher score indicates greater social isolation (Table 1).

**Mortality**

As described in our previous papers [49, 50], information on causes of death up to December 31, 2019, was obtained via record linkage with the Death Registry of the Center for Disease Control and Prevention in Guangzhou. Causes of death were coded according to the 10th Revisions of the International Classification of Diseases (ICD-10) by trained clinical coding officers in each hospital. The
ICD-10 codes of the cause-specific mortality were as follows: cardiovascular disease (I00-I99, excluding I26, I27), cancer (C00-C96), and other diseases (all remaining ICD-10 codes). A physician panel including 5 chief physicians from various disciplines reviewed all available medical records of the same individuals and assigned in a standard manner a cause of death, with the assistance of an epidemiologist in the last meeting for unsettled cases.
Potential confounders
To examine the extent to which baseline socioeconomic position (SEP), biological, behavioral, and psychological factors explained the associations, we included them in two models. Sex, age, and self-rated health (good/very good, poor/very poor) were included in minimal model. The fully adjusted model was adjusted for thirteen factors (sex, age, self-rated health, SEP, biological and behavioral factors): (1) SEP: education (primary and below, middle school, and college or above), occupation (manual, non-manual, and others), family income (≤30,000 CNY/year, >30,000 CNY/year, and not known, US$1 = 7 CNY); (2) biological factors: height and weight were measured, and body mass index (BMI) was calculated by weight in kilogram divided by height in meters squared (kg/m²). After an initial 5-min rest, seated blood pressure was measured 3 times at 1–5 min’s intervals using an Omron 705CP sphygmomanometer (Omron Corp, Kyoto, Japan). Systolic and diastolic blood pressure (SBP and DBP) were calculated as the average of the last 2 measurements. Fasting glucose was measured after an overnight fast; (3) behavioral factors: smoking status (never, former and current), alcohol use (never, former, and current drinkers), physical activity assessed by International Physical Activity Questionnaire (inactive, moderate, and active) [46]; (4) psychological factors: stress level assessed by Perceived Stress Scale-14 items (PSS-14) [51], and cognitive function assessed by Delayed Word Recall Test (DWRT) [52]. The DWRT was assessed in the full data set, but PSS-14 was only assessed in a subsample of GBCS in phrases 1 and 2 (n = 19,947). All potential confounders were categorized as in Table 2. We calculated the percentage of excess risk mediated (PERM), which represented the percentage of risks that explained by SEP, and biological and behavioral factors as in the two previous UK Biobank papers [5, 32]:

\[
\text{PERM} = \frac{[\text{Hazard ratio (minimally adjusted)} - \text{hazard ratio (fully adjusted adjusted)}]}{\text{Hazard ratio(minimally adjusted)}} \times 100\%
\]

Statistical analysis
Chi-square test or analysis of variance was used to compare baseline characteristics by four types of social isolation. Associations of four types of social isolation with all-cause and cause-specific mortality were estimated by Cox proportional hazards model giving hazard ratios (HRs) and 95% confidence intervals (CI). Schoenfeld’s residuals were used to assess the proportional hazard assumption, and no major violations were observed. In sensitivity analysis, competing risk analysis (Fine-Gray’s model) [53] were used to assess the association of social isolation with cause-specific mortality, where each cause was simultaneously modeled as a different event. In sensitivity analysis, fully adjusted model was additionally adjusted for psychological factors using the subgroup dataset because PSS-14 data were available in the subsample only. To explore potential bias due to missing data, we assessed the proportion of missing data for all variables. The proportion of missing data in all variables was very low (i.e., less than 3%) (Additional file 1: Table S2). Therefore, we used complete case analysis in the current study. Subgroup analyses were done by sex, age groups (<60 years, ≥60 years), education (≤primary, ≥middle school), and self-rated health (poor/very poor, good/very good) to investigate whether the associations of social isolation with mortality varied by these factors [32, 54, 55]. For sensitivity analysis, in order to assess the independent associations of face-to-face and non-face-to-face isolation with mortality, we analyzed the associations of 3 types of contact (excluding club/organization isolation which showed no association with mortality) with all-cause mortality after mutual adjustment in a sensitivity analysis. To partly address reverse causation, we excluded participants who died within the first 2 years in the main analysis and provided the original data (without excluding death within first 2 years) analysis for comparability. Also, a subsample of 18,104 participants who returned for repeated examination during 2008–2012 was analyzed to examine the associations in survivors after baseline examination. All statistical analyses were done using the Stata version 15.0 (STATA Corp LP). All tests were two-sided, with \( P < 0.05 \) as statistically significant.

Results
During an average follow-up of 13.2 (standard deviation = 2.8) years with 396,466 person-years, of 30,430 participants, 375 who were lost to follow-up with unknown vital status were excluded. We also excluded 244 deaths that occurred within the first 2 years. We then additionally excluded 2688 with self-reported CVD and 571 with self-reported cancer in the analyses of CVD and cancer mortality respectively. Of 29,811 participants included in the all- and other-cause analysis, up to December 2019, 4933 deaths occurred, in which 1340 were other-cause. Of 27,123 participants for CVD mortality analysis, 1565 deaths occurred, and of 29,240 participants for cancer mortality analysis, 1662 deaths occurred (Fig. 2).
| Face-to-face contact with co-inhabitants | ≥ 1 time/month | < 1 time/month | No such contact |
|-----------------------------------------|---------------|---------------|---------------|
| Face-to-face contact with non-co-inhabitants | ≥ 3 people | < 3 people | No such contact |
| Non-face-to-face contact (by telephone/mail) | ≥ 1 time/month | < 1 time/month | No such contact |
| Club/organization contact | ≥ 1 time/month | < 1 time/month | No such contact |

### Baseline characteristics of the participants by four types of social contact isolation in Guangzhou Biobank Cohort study

#### Number of participants

- Face-to-face contact with co-inhabitants: 27,701
- Face-to-face contact with non-co-inhabitants: 1926
- Non-face-to-face contact (by telephone/mail): 647
- Club/organization contact: 26,438
- ≥ 1 time/month: 3582
- < 1 time/month: 160
- No such contact: 23,557

#### Sex, men %

- Face-to-face contact with co-inhabitants: 7332 (26.9)
- Face-to-face contact with non-co-inhabitants: 644 (33.4)
- Non-face-to-face contact (by telephone/mail): 647 (30.6)
- Club/organization contact: 7115 (26.9)
- ≥ 1 time/month: 1164 (32.5)
- < 1 time/month: 58 (36.3)
- No such contact: 6199 (26.3)

#### Age, years, mean (SD)

- Face-to-face contact with co-inhabitants: 61.9 (7.0)
- Face-to-face contact with non-co-inhabitants: 62.9 (7.7)
- Non-face-to-face contact (by telephone/mail): 64.3 (7.9)
- Club/organization contact: 61.8 (7.1)
- ≥ 1 time/month: 62.9 (7.1)
- < 1 time/month: 63.8 (7.7)
- No such contact: 62.9 (7.1)

#### Self-rated health, good/very good, %

- Face-to-face contact with co-inhabitants: 22,183 (82.9)
- Face-to-face contact with non-co-inhabitants: 1397 (75.7)
- Non-face-to-face contact (by telephone/mail): 418 (69.7)
- Club/organization contact: 21,498 (83.0)
- ≥ 1 time/month: 2676 (83.8)
- < 1 time/month: 108 (69.7)
- No such contact: 19,270 (83.5)

#### Socioeconomic position

| Education, % | ≤ Primary | Middle | ≥ College |
|--------------|-----------|-------|----------|
| Face-to-face contact with co-inhabitants: 11,459 (42.1) 839 (46.0) 339 (69.1) | 11,138 (42.2) 1707 (47.7) | 11,853 (42.3) 237 (63.5) |
| Face-to-face contact with non-co-inhabitants: 13,262 (48.7) 194 (48.7) 642 (48.7) | 12,902 (48.8) 2142 (48.6) | 11,833 (40.3) 237 (48.6) |
| Non-face-to-face contact (by telephone/mail): 2506 (9.2) 119 (6.2) 463 (72.5) | 2370 (90.5) 38 (78) | 2339 (69.5) |
| Club/organization contact: 16,423 (60.6) 119 (6.2) 463 (72.5) | 15,947 (60.6) 2295 (64.3) | 13,952 (59.6) 3118 (63.7) |
| ≥ 1 time/month: 16,423 (60.6) 119 (6.2) 463 (72.5) | 15,947 (60.6) 2295 (64.3) | 13,952 (59.6) 3118 (63.7) |
| < 1 time/month: 16,423 (60.6) 119 (6.2) 463 (72.5) | 15,947 (60.6) 2295 (64.3) | 13,952 (59.6) 3118 (63.7) |
| No such contact: 16,423 (60.6) 119 (6.2) 463 (72.5) | 15,947 (60.6) 2295 (64.3) | 13,952 (59.6) 3118 (63.7) |

#### Family income, CNY/year, %

- ≤ 30,000: 10,191 (37.5) 826 (43.1) 271 (42.0) | 9978 (37.8) 1409 (39.4) 78 (48.8) |
- > 30,000: 10,534 (38.7) 659 (34.2) 186 (28.8) | 10,207 (38.7) 1250 (34.9) 38 (23.8) |
- Do not know: 6478 (23.9) 436 (22.8) 190 (29.2) | 6290 (23.9) 436 (22.8) 190 (29.2) |

#### Biological factors

| BMI, kg/m², mean (SD) | SBP, mmHg, mean (SD) | DBP, mmHg, mean (SD) | FG, mmol/L, mean (SD) |
|-----------------------|----------------------|----------------------|----------------------|
| Face-to-face contact with co-inhabitants: 27.8 (8.3) 23.7 (3.2) 238 (8.3) | 131 (2.2) 131 (2.2) 131 (2.2) | 131 (2.2) 131 (2.2) 131 (2.2) |
| Face-to-face contact with non-co-inhabitants: 27.8 (8.3) 23.7 (3.2) 238 (8.3) | 131 (2.2) 131 (2.2) 131 (2.2) | 131 (2.2) 131 (2.2) 131 (2.2) |
| Non-face-to-face contact (by telephone/mail): 27.8 (8.3) 23.7 (3.2) 238 (8.3) | 131 (2.2) 131 (2.2) 131 (2.2) | 131 (2.2) 131 (2.2) 131 (2.2) |
| Club/organization contact: 27.8 (8.3) 23.7 (3.2) 238 (8.3) | 131 (2.2) 131 (2.2) 131 (2.2) | 131 (2.2) 131 (2.2) 131 (2.2) |
| ≥ 1 time/month: 27.8 (8.3) 23.7 (3.2) 238 (8.3) | 131 (2.2) 131 (2.2) 131 (2.2) | 131 (2.2) 131 (2.2) 131 (2.2) |
| < 1 time/month: 27.8 (8.3) 23.7 (3.2) 238 (8.3) | 131 (2.2) 131 (2.2) 131 (2.2) | 131 (2.2) 131 (2.2) 131 (2.2) |
### Table 2 (continued)

|                                      | Face-to-face contact with co-inhabitants | Face-to-face contact with non-co-inhabitants | Non-face-to-face contact (by telephone/mail) | Club/organization contact |
|--------------------------------------|------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------|
|                                      | ≥ 3 people | < 3 people | Live alone | ≥ 1 time/m. | < 1 time/m. | No such contact | ≥ 1 time/m. | < 1 time/m. | No such contact | ≥ 1 time/m. | < 1 time/m. |
| **Behavioral factors**               |            |            |            |              |            |                |              |            |                |              |            |            |
| Smoking status, %                    |            |            |            |              |            |                |              |            |                |              |            |            |
| Never                                | 21,171 (81.5) | 1464 (76.2) | 486 (75.4) ** | 21,497 (81.4) | 2757 (77.2) | 109 (68.1) ** | 19,280 (81.9) | 3766 (76.8) | 1317 (77.3) ** | 11,544 (83.3) | 12,776 (78.7) ** |
| Former                               | 2396 (88) | 230 (11.8) | 78 (12.1) | 2350 (8.9) | 393 (11.0) | 21 (13.1) | 2076 (8.8) | 526 (10.7) | 160 (9.4) | 1243 (9.0) | 1517 (9.3) |
| Current                              | 2643 (9.7) | 229 (11.9) | 81 (12.6) | 2569 (9.7) | 423 (11.8) | 30 (18.8) | 2180 (9.3) | 615 (12.5) | 226 (13.3) | 1070 (7.7) | 1945 (12.0) |
| Alcohol use, %                       |            |            |            |              |            |                |              |            |                |              |            |            |
| Never                                | 19,926 (73.5) | 1205 (62.9) | 315 (50.2) ** | 19,152 (72.8) | 2472 (69.4) | 84 (52.5) ** | 17,093 (72.9) | 3397 (69.6) | 1216 (71.5) ** | 10,114 (73.3) | 11,560 (71.5) ** |
| Former                               | 902 (3.3) | 89 (4.7) | 47 (7.5) | 935 (3.55) | 113 (3.17) | 13 (8.1) | 769 (3.3) | 224 (46) | 69 (41) | 404 (2.9) | 658 (4.1) |
| Current                              | 6285 (23.2) | 621 (32.4) | 267 (42.3) | 6220 (23.6) | 975 (27.4) | 63 (39.4) | 5581 (23.8) | 1259 (25.8) | 417 (24.5) | 3280 (23.8) | 3957 (24.5) |
| Physical activity, %                 |            |            |            |              |            |                |              |            |                |              |            |            |
| Inactive                             | 2242 (83) | 142 (7.3) | 25 (3.8) ** | 2091 (7.9) | 335 (94) | 5 (3.1) ** | 1862 (7.9) | 450 (92) | 117 (6.9) ** | 653 (4.7) | 1778 (10.9) ** |
| Minimally active                     | 11,382 (41.8) | 657 (34.1) | 132 (20.4) | 10,880 (41.2) | 1385 (38.7) | 63 (39.4) | 9439 (40.1) | 2099 (42.7) | 790 (46.3) | 5006 (36.1) | 7308 (45.0) |
| Active                               | 13,607 (50.0) | 1127 (58.5) | 490 (75.7) | 13,467 (50.9) | 1862 (52.0) | 92 (57.5) | 12,256 (52.0) | 2364 (48.1) | 800 (46.9) | 8214 (59.2) | 7167 (44.1) |
| **Psychological factors**            |            |            |            |              |            |                |              |            |                |              |            |            |
| Stress level (PSS-14), mean (SD)     | 14.7 (4.3) | 15.8 (4.5) | 16.8 (5.0) ** | 14.7 (4.3) | 14.8 (4.6) | 15.6 (5.4) ** | 14.7 (4.2) | 14.9 (4.6) | 1.54 (5.1) ** | 14.9 (4.2) | 14.6 (4.4) ** |
| Cognitive function (DWRT), mean (SD) | 5.5 (1.8) | 5.4 (2.0) | 5.3 (2.2) ** | 5.5 (1.8) | 5.3 (1.9) | 4.6 (2.3) ** | 5.6 (1.8) | 5.4 (1.8) | 5.0 (2.0) ** | 56 (1.8) | 5.4 (1.9) ** |

*CNY* Chinese Yuan Renminbi (US$1 = 7 CNY), *PSS-14* Perceived Stress Scale-14 items, *DWRT* Delayed Word Recall Test, *SD* standard deviation, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FG* fasting glucose

*P < 0.05; **P < 0.001*
Table 2 shows that those who were socially isolated (i.e., with less contact in all groups) were older and fewer had good/very good health status. More men were isolated with non-co-inhabitants and club/organization. Social isolation from face-to-face contact with co-inhabitants and non-co-inhabitants was associated with lower SEP (lower education, manual occupation, and lower family income), more smoking and alcohol use, and higher physical activity. Participants with less non-face-to-face contact and club/organization contact showed similar patterns but had lower physical activity. Moreover, those with less social contact had higher PSS-14 (stress level) and lower DWRT (cognitive function) scores.

Figures 3 and 4 show the minimal adjust HR and fully adjusted HR with 95% CI of four types of social isolation with all-cause and cause-specific mortality. In Fig. 3, participants who lived alone had higher risks of all-cause (adjusted hazard ratio (AHR) = 1.24; 95% CI 1.04 to 1.49, \( P \) for trend < 0.001) and CVD (1.61; 1.20–2.03, \( P \) for trend = 0.001) mortality than those who had \( \geq 3 \) co-inhabitant contact. Compared with those who had \( \geq 1 \) time/month non-co-inhabitant contact, those without such contact had higher risks of all-cause (1.60; 1.20–2.00, \( P \) for trend = 0.008) and CVD (1.91; 1.20–2.62, \( P \) for trend = 0.008) mortality. The corresponding AHR (95% CI, \( P \) for trend) in participants without telephone/mail contact were 1.27 (1.14–1.42, < 0.001) and 1.30 (1.08–1.56, 0.009). In Fig. 4, no association of all four types of isolation with cancer mortality was found, but “<3 people” with co-inhabitants (1.23;
### A. All-cause mortality

| Contact Type                                      | Participants (cumulative mortality) | Minimally adjusted HR | Fully adjusted HR |
|--------------------------------------------------|-------------------------------------|-----------------------|-------------------|
| Face-to-face contact with co-inhabitants         |                                     |                       |                   |
| ≥ 3 people                                       | 26,902 (16.3%)                      | 1.00                  | 1                 |
| < 3 people                                       | 1,891 (21.6%)                       | 1.22                  | 1.17 (1.05-1.30)  | 23%               |
| Live alone                                       | 634 (22.1%)                         | 1.28                  | 1.24 (1.04-1.49)  | 14%               |
| Face-to-face contact with non-co-inhabitants     |                                     |                       |                   |
| ≥ 1 time /month                                  | 25,841 (16.1%)                      | 1.00                  | 1                 |
| < 1 time/month                                   | 3,494 (18.7%)                       | 1.09                  | 1.07 (0.98-1.16)  | 22%               |
| No such contact                                  | 154 (32.5%)                         | 1.73                  | 1.60 (1.20-2.00)  | 18%               |
| Non-face-to-face contact (by telephone/mail)    |                                     |                       |                   |
| ≥ 1 time /month                                  | 23,034 (15.7%)                      | 1.00                  | 1                 |
| < 1 time/month                                   | 4,802 (18.2%)                       | 1.09                  | 1.04 (0.97-1.11)  | 56%               |
| No such contact                                  | 1,650 (24.1%)                       | 1.35                  | 1.27 (1.14-1.42)  | 23%               |
| Club/organization contact                        |                                     |                       |                   |
| ≥ 1 time /month                                  | 13,525 (18.3%)                      | 1.00                  | 1                 |
| < 1 time/month                                   | 15,910 (15.0%)                      | 1.03                  | 1.00 (0.94-1.06)  | 100%              |
| Composite social isolation score                 | 0~7                                 | 1.11                  | 1.09 (1.05-1.13)  | 18%               |

### B. CVD-cause mortality

| Contact Type                                      | Participants (cumulative mortality) | Minimally adjusted HR | Fully adjusted HR |
|--------------------------------------------------|-------------------------------------|-----------------------|-------------------|
| Face-to-face contact with co-inhabitants         |                                     |                       |                   |
| ≥ 3 people                                       | 25,240 (5.4%)                       | 1.00                  | 1                 |
| < 3 people                                       | 1,754 (7.9%)                        | 1.28                  | 1.19 (0.99-1.42)  | 37%               |
| Live alone                                       | 592 (9.6%)                          | 1.67                  | 1.61 (1.20-2.03)  | 9%                |
| Face-to-face contact with non-co-inhabitants     |                                     |                       |                   |
| ≥ 1 time /month                                  | 23,930 (5.6%)                       | 1.00                  | 1                 |
| < 1 time/month                                   | 3,190 (6.2%)                        | 1.03                  | 0.99 (0.85-1.15)  | -                 |
| No such contact                                  | 138 (13.8%)                         | 2.05                  | 1.91 (1.20-2.62)  | 13%               |
| Non-face-to-face contact (by telephone/mail)    |                                     |                       |                   |
| ≥ 1 time /month                                  | 21,282 (5.3%)                       | 1.00                  | 1                 |
| < 1 time/month                                   | 4,415 (6.3%)                        | 1.11                  | 1.02 (0.89-1.17)  | 82%               |
| No such contact                                  | 1,561 (8.9%)                        | 1.42                  | 1.30 (1.08-1.56)  | 29%               |
| Club/organization contact                        |                                     |                       |                   |
| ≥ 1 time /month                                  | 12,477 (6.3%)                       | 1.00                  | 1                 |
| < 1 time/month                                   | 14,733 (5.1%)                       | 1.09                  | 1.05 (0.94-1.16)  | 44%               |
| Composite social isolation score                 | 0~7                                 | 1.14                  | 1.09 (1.04-1.15)  | 36%               |

Fig. 3 (See legend on previous page.)
thirteen factors. However, isolation from club/organization contact was associated with higher other-cause mortality. No telephone/mail contact was also associated with higher other-cause mortality (1.37, 1.12–1.67, P for trend = 0.006). Furthermore, an increase in one composite social isolation score was associated with 9%, 9%, and 12% higher risk of all-cause, CVD-, and other-cause mortality respectively, with PERM showing 18%, 36%, and 20% risk explained by the thirteen factors. However, isolation from club/organization contact was not associated with the above mortality. The competing risk analyses (Additional file 1: Table S3) shows similar results as those from the main analysis using traditional Cox regression (Figs. 3 and 4).

In sensitivity analyses of the subsample of 19,947 participants, AHR for all-cause, CVD-, and other-cause mortality after additional adjustment for psychological factors in fully adjusted model become higher in those who lived alone, but attenuated for face-to-face with non-co-inhabitants and composite social isolation score (Additional file 1: Table S4). Almost all P values for test of interaction by sex, age, education, and health status on the associations of mortality and social isolation were not significant, and the few with P < 0.05 have become non-significant if multiple testing were accounted for (Additional file 1: Table S5-8). The face-to-face contact with co-inhabitants, non-co-inhabitants, and non-face-to-face contact remained positively associated with all-cause mortality after mutual adjustment, although the estimates were slightly attenuated (Additional file 1: Table S9). There are only slightly change before and after death within the first 2 years (Additional file 1: Table S10 compared with Fig. 3 which have excluded 244 deaths within first 2 years). The Kaplan-Meier survival curves show that the more severe social isolation was associated with lower survival probability in both baseline (2003–2008) and repeated (2008–2012) examination (Additional file 1: Fig S1 and S2).

**Discussion**

**Principal findings**

We have first, in a long-term prospective study (with about 13 years follow-up), show the positive associations of face-to-face and non-face-to-face isolation and a composite isolation score, with all-cause, CVD- and other-cause (but not cancer) mortality. Only 18–36% of the excess risk was attributable to the known risk factors such as SEP, biological, and behavioral factors. No association of club/organization contact (< 1 time/month versus ≥ 1 time/month) with all-cause and cause-specific mortality was found.

**Comparison with other studies**

Our findings are in line with previous studies showing social isolation was associated with a higher risk of all-cause and CVD mortality [8, 13, 24, 32]. However, no previous studies reported the associations with face-to-face isolation and non-face-to-face isolation separately. For example, the UK Biobank study [32] assessed social isolation using a social isolation index, which only included questions on face-to-face contact. The Million Women Study [3] and English Longitudinal Study of Ageing [54] included results of a composite score with e-mail, phone and face-to-face contact but did not report results on different isolation types. The Whitehall II Study [55], the Nurses’ Health Study [56], and the Heinz Nixdorf Recall Study [24] also showed a higher mortality risk related to social isolation but did not specify the types of contact. Therefore, our study has provided additional evidence that both face-to-face and non-face-to-face isolation are associated with increased mortality risk. Our results on non-face-to-face contact are also consistent with a prospective study showing that participants with online social media experience (Facebook use) had a lower risk of mortality during two years follow-up than those without [57]. However, this study did not report the association of face-to-face contact with mortality, and the association of non-face-to-face contact was not adjusted for SEP and behavioral factors.

Furthermore, whether the associations of social isolation with mortality varied by sex, age, education, and health status is inconclusive [6, 18, 32, 54]. We found consistent associations of social isolation with all-cause, CVD-, and other-cause mortality after adjustment for sex, age, education, and health status. Our sex-stratified results are not consistent with one previous study showing the stronger associations of social isolation with CVD in women than men [32], neither consistent with other two reported stronger associations in men [24, 58]. We found the education did not modify the associations of social isolation with mortality, which was not consistent with previous studies showing the mortality risk of social isolation change
### A. Cancer-cause mortality

| Contact Type                                      | Participants (cumulative mortality) | Minimally adjusted HR | Fully adjusted HR | PERM adjusted HR |
|--------------------------------------------------|-------------------------------------|-----------------------|-------------------|------------------|
| Face-to-face contact with co-inhabitants         |                                     |                       |                   |                  |
| ≥ 3 people                                       | 27,184 (5.6%)                       | 1.00                  | 1                 |                  |
| < 3 people                                       | 1,886 (6.2%)                        | 1.06                  | 1.05 (0.87-1.24)  | 17%              |
| Live alone                                       | 633 (5.5%)                          | 1.00                  | 1.01 (0.71-1.33)  | -                |
| Face-to-face contact with non-co-inhabitants     |                                     |                       |                   |                  |
| ≥ 1 time /month                                  | 25,722 (5.5%)                       | 1.00                  | 1                 |                  |
| < 1 time/month                                   | 3,494 (5.8%)                        | 0.98                  | 0.98 (0.84-1.14)  | -                |
| No such contact                                  | 152 (9.2%)                          | 1.53                  | 1.36 (0.79-1.93)  | 32%              |
| Non-face-to-face contact (by telephone/mail)     |                                     |                       |                   |                  |
| ≥ 1 time /month                                  | 22,924 (5.4%)                       | 1.00                  | 1                 |                  |
| < 1 time/month                                   | 4,779 (6.0%)                        | 1.04                  | 1.02 (0.89-1.16)  | 50%              |
| No such contact                                  | 1,663 (6.8%)                        | 1.18                  | 1.14 (0.93-1.39)  | 22%              |
| Club/organization contact                        |                                     |                       |                   |                  |
| ≥ 1 time /month                                  | 13,450 (6.2%)                       | 1.00                  | 1                 |                  |
| < 1 time/month                                   | 15,865 (5.1%)                       | 0.94                  | 0.90 (0.81-1.00)  | -                |
| Composite social isolation score                 | 0~7                                 | 29,143 (5.6%)         | 1.04              | 1.03 (0.97-1.09) | 25%              |

### B. Other-cause mortality

| Contact Type                                      | Participants (cumulative mortality) | Minimally adjusted HR | Fully adjusted HR | PERM adjusted HR |
|--------------------------------------------------|-------------------------------------|-----------------------|-------------------|------------------|
| Face-to-face contact with co-inhabitants         |                                     |                       |                   |                  |
| ≥ 3 people                                       | 27,701 (4.3%)                       | 1.00                  | 1                 |                  |
| < 3 people                                       | 1,926 (6.3%)                        | 1.29                  | 1.23 (1.01-1.50)  | 21%              |
| Live alone                                       | 647 (6.3%)                          | 1.36                  | 1.30 (0.93-1.70)  | 17%              |
| Face-to-face contact with non-co-inhabitants     |                                     |                       |                   |                  |
| ≥ 1 time /month                                  | 26,233 (4.2%)                       | 1.00                  | 1                 |                  |
| < 1 time/month                                   | 3,549 (5.7%)                        | 1.28                  | 1.24 (1.07-1.45)  | 14%              |
| No such contact                                  | 156 (7.7%)                          | 1.54                  | 1.47 (0.83-2.11)  | 13%              |
| Non-face-to-face contact (by telephone/mail)     |                                     |                       |                   |                  |
| ≥ 1 time /month                                  | 23,379 (4.1%)                       | 1.00                  | 1                 |                  |
| < 1 time/month                                   | 4,871 (4.9%)                        | 1.10                  | 1.06 (0.92-1.23)  | 40%              |
| No such contact                                  | 1,686 (7.1%)                        | 1.48                  | 1.37 (1.12-1.67)  | 23%              |
| Club/organization contact                        |                                     |                       |                   |                  |
| ≥ 1 time /month                                  | 13,755 (5.0%)                       | 1.00                  | 1                 |                  |
| < 1 time/month                                   | 16,130 (4.0%)                       | 1.05                  | 1.01 (0.90-1.13)  | 80%              |
| Composite social isolation score                 | 0~7                                 | 29,710 (4.4%)         | 1.15              | 1.12 (1.06-1.19) | 20%              |

**Fig. 4** (See legend on previous page.)
depend upon SEP but without clarifying the types of social contact [27, 59, 60]. Moreover, living alone was particularly increased the CVD mortality in unhealthy participants suggesting the importance of immediate help among people who live alone, as a recent study reported [3].

Socially integrated people usually have more access to resources for health-promoting behavioral and chronic disease management [61]. Our results suggest that 18–36% of the excess all-cause, CVD-, and other-cause mortality risks could be attributable to SEP, biological, and behavioral factors, which is lower than those reported in two previous studies [5, 32], which showed that 64% and 84% mortality risk were explained by confounders or mediators. The fraction of excess risk remaining unexplained indicates some biological mechanisms beyond traditional pathways. For example, individuals with greater social support might have better immune function [62, 63]. Other pathways such as neuroendocrine mechanisms might also play a role [64, 65]. A recent genome-wide association study (GWAS) identified 38 significant genetic variants for social interaction, highlighting the possible genetic basis for social isolation [66]. Furthermore, another study found that gene expression differed between socially isolated and non-isolated individuals [67].

Strengths and limitations
A major strength of the current study was that we, for the first time, analyzed the risk of mortality related to four important social isolation types: face-to-face isolation from co-inhabitants, face-to-face isolation from non-co-inhabitants, non-face-to-face isolation, and club/organization isolation, and provided the independent associations of face-to-face isolation and non-face-to-face isolation after mutual adjustment, which have never been reported in previous studies. The comprehensive analyses of four aspects of social isolation are essential because social contact patterns have been changing given the social-economic development. Our results demonstrated the beneficial role of non-face-to-face contact, which, if causal, would have important public health implications, although virtual contact has been the dominant form for non-face-to-face contact nowadays. Other strengths of our study included the long-term follow-up and the comprehensive adjustment for potential confounders. However, some limitations need to be considered. First, as about 98% of participants were retired at the time of baseline examination, workplace contact was not included in our study. Although the absence of workplace contact was unlikely to affect the internal validity of the present study, generalizability of our results to younger populations, in whom workplace contact may represent a major mode of contact, might be limited. Also, the other non-face-to-face contact such as instant message applications (video contact) and e-mail were not included. However, since this cohort study was initiated in 2003, such non-face-to-face contact was not prevalent, especially in older people. Specifically, the new technologies have been found to be effective in social contact for older people, but the findings were often mixed or inconclusive [68, 69]. Further studies are warranted to clarify. Second, we did not assess the effect of loneliness, which is a negative emotional state resulting from isolation, on mortality. However, isolation, which can be measured more objectively, rather than loneliness, was found to be an independent predictor of mortality [5]. Third, as evaluation of social isolation was based on self-report, reporting error was possible, although such error was more likely to be non-differential. Fourth, although residual confounding cannot be completely excluded in observational studies, the adjustment for a wide range of potential confounders in the current study should have minimized this bias. Fifth, reverse causality was possible, but we excluded deaths within 2 years in the main analysis and further conducted subgroup analyses in participants only with self-rated good/very good health status with no substantial changes in the original results. Sixth, we assessed social isolation at baseline and did not account for the changes in social isolation during the follow-up [70]. However, our sensitivity analysis of a subgroup of 18,104 participants who returned for repeated examination during 2008–2012 showed similar results to the main analyses (Additional file 1: Fig S1-2). Finally, as all GBCS participants were middle-aged and older Chinese, generalizability of our results to other populations or younger age groups may be limited.

Conclusions
From a public health perspective, in the absence of well-designed trials of interventions to decrease social isolation with mortality as an outcome [71], our results suggest that people with face-to-face and non-face-to-face isolation both need more special attention and follow-up. Our findings, if causal, emphasize the importance of policies to test the effective way of increasing not only face-to-face but also non-face-to-face contact to promote physical and mental health.

Abbreviations
AHR: Adjusted hazard ratio; CVD: Cardiovascular disease; COVID: Coronavirus disease; GBCS: Guangzhou biobank cohort study; HAPIER: Guangzhou Health and Happiness Association for the Respectable Elders; CNY: Chinese yuan renminbi; US: United States; SNI: Social Network Index; ICD: International Classification of Diseases; SEP: Socioeconomic position; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PSS-14: Perceived Stress Scale-14 items; DWRT: Delayed Word Recall Test; PERM: Percentage of excess risk mediated; HR: Hazard ratios; CI: Confidence intervals; GWAS: Genome-wide association study.
Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-022-02368-3.

Additional file 1: Table S1. Summary information for studies about the associations of social isolation with all-cause mortality (from Jan 2015 to May 2021). Table S2. The missing percent of the variables in the cohort. Table S3. Associations of social isolation with cause-specific mortality using competing risk model (Fine-Gray’s model). Table S4. Associations of social isolation with all-cause and cause-specific mortality with additional adjustment for psychological factors in the subgroup (n=19,947). Table S5. Associations of social isolation with all-cause and cause-specific mortality by sex (men, women). Table S6. Associations of social isolation with all-cause and cause-specific mortality by age group (< 60 years, ≥60 years). Table S7. Associations of social isolation with all-cause and cause-specific mortality by education group (< primary, ≥ middle school). Table S8. Associations of social isolation with all-cause and cause-specific mortality by health status (poor/very poor, good/very good). Table S9. Associations of face-to-face and non-face-to-face contact with all-cause mortality after mutual adjustment of 3 types of contact. Table S10. Associations of social isolation with all-cause mortality in original dataset (without excluding 244 death within first 2 years).

Figure S1. Kaplan–Meier survival curve by four types of social isolation assessed at baseline examination (2003-2008) for all-cause mortality in 30,430 participants. Figure S2. Kaplan–Meier survival curve by four types of social isolation assessed at follow-up examination (2008-2012) for all-cause mortality in 18,104 participants.

Acknowledgements
The Guangzhou Biobank Cohort Study investigators include the following: Guangzhou No. 12 Hospital: WS Zhang, M Cao, T Zhu, B Liu, CQ Jiang (Co-PI); The University of Hong Kong: CM Schooling, SM McGhee, GM Leung, R Fielding, TH Lam (Co-PI); The University of Birmingham: P Adab, GN Thomas, KK Cheng (Co-PI).

Authors’ contributions
JW, LX, THL, CQJ, WSZ, FZ, YLJ, and KKC have substantial contributions to conception and design, acquisition of funding, and data and interpretation of data; JW and LX analyzed the data; JW, LX, THL, and CQJ drafted the article; THL, LX, and WSZ revised it critically for important intellectual content; WSZ and LX are the guarantors. All authors read and approved the final manuscript.

Funding
This work was funded by the National Natural Science Foundation of China (82103930) and Natural Science Foundation of Guangdong (2022A1515011546). The Guangzhou Biobank Cohort Study was funded by the University of Hong Kong Foundation for Educational Development and Research (SN/16/486/OC, C204002.28505200), the Health Medical Research Fund (Grant number: HnRF/13143241) in Hong Kong, Guangzhou Public Health Bureau (201102A21100401), and the University of Birmingham, UK. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Availability of data and materials
Ethical approval in place allows us to share data on requests. Please directly send such requests to the Guangzhou Biobank Cohort Study Data Access Committee (gbcidata@hku.hk).

Declarations

Ethics approval and consent to participate
The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study (ethics approval ID: 2021047), and all participants gave written, informed consent before participation.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 School of Public Health, Sun Yat-sen University (North Campus), No. 74, 2nd Zhongshan Road, Guangzhou, Guangdong, China. 2 Guangzhou Twelfth People’s Hospital, Guangzhou, China. 3 Institute of Applied Health Research, University of Birmingham, Birmingham, UK. 4 School of Public Health, The University of Hong Kong, Hong Kong, China.

Received: 13 December 2021 Accepted: 6 April 2022

Published online: 02 May 2022

References
1. Nicholson NR Jr. Social isolation in older adults: an evolutionary concept analysis. J Adv Nurs. 2009;56(6):1342–52.
2. Nicholson NR. A review of social isolation: an important but underassessed condition in older adults. J Prim Prev. 2012;33(2):137–52.
3. Smith RW, Barnes I, Green J, Reeves GK, Beral V, Foulard S. Social isolation and risk of heart disease and stroke: analysis of two large UK prospective studies. Lancet Public Health. 2021;6(4):e232–9.
4. Desai R, John A, Stott J, Charlesworth G. Living alone and risk of dementia: a systematic review and meta-analysis. Ageing Res Rev. 2020;62:101122.
5. Elovainio M, Hakulinen C, Pulkki-Råback L, Virtanen M, Jokela M, et al. Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study. Lancet Public Health. 2017;2(6):e260–6.
6. Pantell M, Rehkopf D, Jutte D, Syme SL, Balmes J, Adler N. Social isolation: a predictor of mortality comparable to traditional clinical risk factors. Am J Public Health. 2013;103(11):2056–62.
7. National Academies of Sciences E. Medicine: Social isolation and loneliness in older adults: opportunities for the health care system. Washington, DC: The National Academies Press; 2020.
8. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 2010;7(7):e1000316.
9. Cudjoe TKM, Roth DL, Szanton SL, Wolf JL, Boyd CM, Thorpe RJ. The epidemiology of social isolation: national health and aging trends study. J Gerontol Ser B Psychol Sci Soc Sci. 2020;75(1):107–13.
10. Kotian DB, Mathews M, Parisek SS, Nair S, Binu VS, Subba SH. Factors associated with social isolation among the older people in India. J Geriatr Psychiatry Neuro. 2018;31(5):271–8.
11. Wu F, Sheng Y. Differences in social isolation between young and old elderly in urban areas of Beijing, China: a cross-sectional study. Int J Nurs Sci. 2020;7(1):49–53.
12. Escalante E, Golden RL, Mason DJ. Social isolation and loneliness: imperatives for health care in a post-COVID world. JAMA. 2021;325(6):520–1.
13. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspect Psychol Sci. 2015;10(2):227–37.
14. Shor E, Roelfs DJ. Social contact frequency and all-cause mortality: a meta-analysis and meta-regression. Soc Sci Med. 2015;128:76–86.
15. Crowe CL, Domingue BW, Graf GH, Keyes KM, Kwan D, Belsky DW. Associations of loneliness and social isolation with health span and life span in the US health and retirement study. J Gerontol A Biol Sci Med Sci. 2020;76(11):1997–2006. https://doi.org/10.1093/gerona/glaba128.
16. Kraav SL, Awoyemi O, Junttila N, Vornanen R, Kauhanen J, Toikko T, et al. Impact of social isolation on mortality and morbidity in 20 high-income, middle-income and low-income countries in five continents. BMJ Glob Health. 2021;6(5):e004124. https://doi.org/10.1136/bmjgh-2020-004124.

1 School of Public Health, Sun Yat-sen University (North Campus), No. 74, 2nd Zhongshan Road, Guangzhou, Guangdong, China. 2 Guangzhou Twelfth People’s Hospital, Guangzhou, China. 3 Institute of Applied Health Research, University of Birmingham, Birmingham, UK. 4 School of Public Health, The University of Hong Kong, Hong Kong, China.
19. Uhing A, Williams JS, Garacco E, Egede LE. Gender differences in the relationship between social support and strain and mortality among a national sample of adults. J Behav Med. 2021;44(5):673–81.

20. Ward M, May P, Normand C, Kenny RA, Nolan A. Mortality risk associated with combinations of loneliness and social isolation findings from the Irish Longitudinal Study on Ageing (TILDA). Age Ageing. 2021;50(4):1329–35.

21. Saito M, Aida J. Cross-national comparison of social isolation and mortality among older adults: a 10-year follow-up study in Japan and England. Geriatr Gerontol Int. 2021;21(2):209–14.

22. Uzuki T, Konta T. Relationship between social support status and mortality in a community-based population: a prospective observational study (Yamagata study). BMC Public Health. 2020;20(1):1630.

23. Gilmour H, Ramage-Morin PL. Social isolation and mortality among Canadian seniors. Health Rep. 2020;33(1):27–38.

24. Gronowold J, Koppel R, Lehmann N, Schmidt B, Weyers S, Siegrist J, et al. Association of social relationships with incident cardiovascular events and all-cause mortality. Heart. 2020;106(17):1317–23.

25. Ng N, Santos A, Weinhal L, Malmberg G. Living alone and mortality among older people in Västerbotten County in Sweden: a survey and register-based longitudinal study. BMC Geriatr. 2020;20(1):7.

26. Trudel-Fitzgerald C, Zevon ES, Kawachi I, Tucker-Seeley RD, Grodstein F, Kubzansky LD. The prospective association of social integration with life span and exceptional longevity in women. J Gerontol Ser B Psychol Sci Soc Sci. 2020;75(10):2132–41.

27. Palacios-Mayoa C, Saimi M, Kivimäki M, Kubzansky LD, Kawachi I. Life span and exceptionally long lives in women: the relationship with social contact and network size. Br J Nutr. 2020;124(8):1232–40.

28. Freeborne N, Simmens SJ, Manson JE, Howard BV, Cené CW, Allison MA, et al. Perceived social support and the risk of cardiovascular disease and all-cause mortality in the Women’s Health Initiative Observational Study. Menopause (New York, NY). 2019;26(7):698–707.

29. Tanaka H, Miyawaki A, Toyokawa S, Kobayashi Y. Relationship of relative supply of social support as risk factor for mortality in the older adults. Arch Gerontol Geriatr. 2017;73:77–81.

30. Hadzi-Pavlovic D, Shrestha AN, Umemori Y, Kubzansky LD, Kawachi I. Social support and loneliness. Exp Gerontol. 2017;99:120–6.

31. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch I, Gottdiener J, et al. The impact of nephropathy on mortality in the Cardiovascular Health Study: the Atherosclerosis Risk in Communities (ARIC) Study and the MESA Study. Arch Intern Med. 2013;173(1):57–64.

32. Hakulinen C, Pulkki-Råback L, Virtanen M, Jokela M, Kivimäki M, Elovainio M. Health-related lifestyle factors and all-cause mortality among younger aged adults in Finland. Ann Epidemiol. 2016;26(4):261–6.

33. Uchino BN, Kiecolt-Glaser JK. Psychological stressors, stress-coping processes, and all-cause mortality in a community-based population: evidence from the Cardiovascular Health Study (CHS). Arch Intern Med. 2003;163(3):274–8.

34. Alcaraz KI, Eddens KS, Blase JL, Diver WR, Patel AV, Teras LR, et al. Social isolation and loneliness. J Gerontol B Psychol Sci Soc Sci. 2018;73(11):1342–51.

35. Honda K, Harada K, Sasayama S, Oishi S, Kusumoto F, Tsuruta Y, et al. Social support and loneliness in Japanese older adults: a cross-sectional study in Japan. J Psychosom Res. 2016;83(2):116–22.

36. Kauppi M, Kawachi I, Batty GD, Oksanen T, Elovainio M, Pentti J, et al. Characteristics of social networks among older adults in Finland: the Cardiovascular Health Study and the MESA Study. J Gerontol B Psychol Sci Soc Sci. 2019;74(6):995–1002.

37. Cross-sectional study of social isolation and resilience in older adults: the Cardiovascular Health Study and the Midtown Manhattan Community Study. J Gerontol B Psychol Sci Soc Sci. 2019;74(6):976–85.

38. de Brito TRP, Nunes DP, Corona LP, da Silva AT, da Silva AT, Barbosa J. Low income and social isolation findings from the Brazilian Longitudinal Study on Aging (Brazil Longitudinal Study on Aging). Int J Geriatr Psychopharmacol. 2020;16:1080–7.

39. Carenini K, Bonsignore M, Stancanelli A, Carinci F. Social isolation and resilience in older adults: the Cardiovascular Health Study and the MESA Study. J Gerontol B Psychol Sci Soc Sci. 2019;74(6):995–1002.

40. Santos H, Santos A, Weinhal L, Malmberg G. Living alone and mortality among older people in Västerbotten County in Sweden: a survey and register-based longitudinal study. BMC Geriatr. 2020;20(1):7.
65. Cacioppo JT, Cacioppo S, Capitanio JP, Cole SW. The neuroendocrinology of social isolation. Annu Rev Psychol. 2015;66:733–67.
66. Day FR, Ong KK, Perry JR.B. Elucidating the genetic basis of social interaction and isolation. Nat Commun. 2018;9(1):2457.
67. Cole SW, Hawkley LC, Arevalo JM, Sung CY, Rose BM, Cacioppo JT. Social regulation of gene expression in human leukocytes. Genome Biol. 2007;8(9):R189.
68. Ibarra F, Baez M, Cernuzzi L, Casati F. A systematic review on technology-supported interventions to improve old-age social wellbeing: loneliness, social isolation, and connectedness. J Healthcare Eng. 2020;2020:2036842.
69. Chen YR, Schulz PJ. The effect of information communication technology interventions on reducing social isolation in the elderly: a systematic review. J Med Internet Res. 2016;18(1):e18.
70. Cohen S, Underwood LG, Gottlieb BH. Social support measurement and interventional guide for health and social scientists: a guide for health and social scientists: Oxford University Press; 2015.
71. Newman MG, Zainal NH. The value of maintaining social connections for mental health in older people. Lancet Public Health. 2020;5(1):e12–3.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.