

Original Research Article

Title: Frailty and all-cause and cause-specific mortality in Japan

Rumi Matsuo MD ^a, Naomi Matsumoto MD PhD ^a, Toshiharu Mitsuhashi MD PhD ^a,
Soshi Takao MD PhD ^a, and Takashi Yorifuji MD PhD ^a

^a Department of Epidemiology, Graduate School of Medicine, Dentistry and
Pharmaceutical Sciences, Okayama University, Okayama, Japan

Corresponding author: Rumi Matsuo

Department of Epidemiology, Graduate School of Medicine, Dentistry and
Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama,
700-8558, Japan

Tel: +81-86-235-7173

E-mail: pkjg52ww@s.okayama-u.ac.jp

Running title: Frailty and cause-specific mortality in Japan

Data: The data are not available to other researchers because we do not have any right
to disclose them.

ABSTRACT

Background: In aging societies, there is an increasing focus on the concept of frailty. However, there is no consistent means to assess this concept. We assessed frailty using the Kihon Checklist (KCL), which is widely used in Japan, and examined the association between frailty and all-cause and cause-specific mortality in Japan, the most aged society in the world.

Methods: This was a retrospective cohort study, and we analyzed 43,312 participants aged ≥ 65 years who were enrolled in basic health checkups in Okayama City, Japan. We defined the frailty status of the participants using the KCL. To assess the association of frailty status with all-cause and cause-specific mortality, we used cause-specific Cox proportional hazard models to estimate hazard ratios (HRs), adjusting for individual potential confounders. Mean follow-up time was 9.3 years.

Results: The fully adjusted HR for all-cause mortality was 1.34 (95% confidence interval [CI]: 1.27-1.41) for the prefrail group and 2.22 (95% CI: 2.11-2.33) for the frail group. A similar pattern was observed for cardiovascular disease, respiratory disease, and cancer mortality. Younger people (65–74 years) and women tended to have higher effect estimates than older people (≥ 75 years) and men.

Conclusion: Prefrailty and frailty can increase the risk of both all-cause and cause-specific mortality. Our study suggests that to support frail patients, it could be effective to focus on the prevention and management of cardiovascular and respiratory disease, and that the KCL may be useful as a method of screening for frailty.

Key words:

prefrailty, Kihon Checklist, cardiovascular disease, respiratory disease, cancer

1. Introduction

In aging societies, there is an increasing focus on the concept of frailty (Hoogendijk et al., 2019). Frailty is usually defined as a state of reduced physiological reserve and increased vulnerability to failure to restore homeostasis after a stressor event (Clegg et al., 2013). Frailty is strongly related to various adverse health outcomes, including disabilities, hospital admission and mortality (Clegg et al., 2013). Recent studies have demonstrated that frailty increased risk of cause-specific mortality, especially for cardiovascular disease (Veronese et al., 2017). However, the assessment of frailty was different between previous studies (Fan et al., 2020; Jiang et al., 2017; Lohman et al., 2020).

A standardized instrument for assessing frailty has not yet been established (Hoogendijk et al., 2019), but frailty index and frailty phenotype are widely used as assessment indicators (Cesari et al., 2014; Walston and Bandeen-Roche, 2015). The frailty index is defined as the accumulation of at least 30 nonspecific diseases, deficits, and other symptoms (Rockwood and Mitnitski, 2007; Searle et al., 2008). The frailty phenotype is defined by combinations of five specific symptoms: weakness, low energy expenditure, slowness, weight loss, and exhaustion (Fried et al., 2001). In other words, the frailty index uses conditions as a way to assess frailty, and the frailty phenotype better reflects functions and signs of frailty. Most of the previous studies that examined the association between frailty and cause-specific mortality assessed frailty using the frailty index, but a limited number of studies used the frailty phenotype.

In this study, we assessed frailty using the frailty screening checklist developed in Japan, which is similar to the frailty phenotype. We then evaluated the associations between frailty and all-cause and cause-specific mortality in Japan, the most aged society in the world.

2. Methods

2.1. Study design and participants

This was a retrospective cohort study, and we used a cohort of 76,591 individuals who were enrolled in basic health checkups in Okayama City, Japan, in the fiscal year of 2006 or 2007 (i.e, between April 2006 and March 2008). Okayama City is an urbanized area in the western part of Japan. These basic health checkups were conducted under the Health and Medical Service Act for the Aged and were provided to residents aged ≥ 40 years to screen for medical conditions such as cardiovascular disease. To be eligible for basic health checkups, residents had to be covered by National Health Insurance, which is one of two main types of health insurance system available in Japan. The other is Employee's Health Insurance (employment-based health insurance). About 50.4% of the residents of Okayama City was eligible for the basic health checkups in the fiscal year of 2006 and about 34.2% of the eligible participants participated in these checkups (Okayama Prefecture, 2013). During the checkups, participants self-reported their medical history, self-rated health, lifestyle habits, and physical activity. They also received a physical assessment (height, weight, and blood pressure at rest), blood analysis (complete blood count and biochemical blood tests), urinalysis (urine protein, blood, and sugar), and electrocardiography, which took place in medical facilities.

Of the 76,591 individuals included in the cohort, 54,851 participants who were at least 65 years of age were asked to complete a Kihon Checklist (KCL) as part of the checkup. This is a commonly used indicator to assess frailty status in Japan. We then followed the survival status of the participants until the end of 2016.

2.2. Frailty status

We defined the frailty status of the participants using the KCL. This was developed by the Ministry of Health, Labour and Welfare (MHLW) in Japan and is widely used for frailty screening in Japan (Supplementary Table 1) (Akishita et al., 2022; Satake et al., 2016; Satake et al., 2017; Sewo Sampaio et al., 2016). The KCL is similar to frailty phenotype in assessing phenotypic factors such as weight loss or physical function. It is a simple self-reporting yes/no survey consisting of 25 questions about instrumental activities of daily living (IADL) (five items), physical function (five items), nutritional status (two items), oral function (three items), socialization (two items), cognitive function (three items), and mood (five items). Difficulty with any question is counted as a score in the KCL (score range: 0–25), with higher scores indicating a greater tendency towards frailty. Drawing on previous studies (Satake et al., 2016; Satake et al., 2017), we classified participants into three frailty groups: robust (0–3 points), prefrail (4–7) and frail (≥ 8). The analysis excluded 11,526 participants who did not complete the KCL (Figure 1).

2.3. All-cause and cause-specific mortality

We used all-cause and cause-specific mortality as our main outcomes of interest. After identifying the survival status of the participants, we evaluated causes of death for those who were deceased by linking records to the vital statistics database of the MHLW in Japan.

We selected the following outcomes and defined them using the 10th International Classification of Diseases (ICD-10): cardiovascular disease (CVD) (I00–I99), respiratory disease (J00–J99), and cancer (C00–C97). We also focused on specific

causes of death for each cause-specific mortality as follows: ischemic heart disease (IHD) (I20–I25), heart failure (I50), cerebrovascular disease (I60–I69), lung cancer (C33–C34), colon cancer (C18–C21), gastric cancer (C16), pneumonia and influenza (J10–J22), and aspiration pneumonia (J69). We excluded 13 participants whose survival status was unknown, leaving 43,312 participants for the analysis (Figure 1).

2.4. Statistical analyses

We started by comparing baseline characteristics by frailty group. We also described baseline characteristics by follow-up status (i.e., those alive at the end of follow-up, those who were lost to follow-up, and those who died during the follow-up).

To assess the association of frailty status with all-cause and cause-specific mortality, we calculated the survival probability of all-cause and cause-specific death by frailty status using Kaplan–Meier curves. The differences were evaluated using the log-rank test. We also used cause-specific Cox proportional hazard models to estimate hazard ratios (HRs), adjusting for individual potential confounders. The proportional hazards assumption was assessed using log–log survival plots. We used the frailty category of robust as a reference. For privacy reasons, we could only obtain the month of death. We also did not know the exact dates when the participants underwent the basic health checkup, and therefore assumed that the KCL scores obtained at the checkups reflected the frailty status of the participants in April 2006. Survival was calculated from April 2006 and censored at the month of leaving the study because of death, loss to follow-up (e.g., move to other municipalities), or at the end of follow-up time in December 2016.

We adjusted first for age (continuous) and sex, then for other potential confounders such as current disease status for hypertension (dichotomous) and diabetes

mellitus (dichotomous), alcohol consumption (dichotomous; drinker including both regular and occasional, or non-drinker), smoking status (categorical; current smoker [Brinkman index ≥ 600], current smoker [Brinkman index < 600], or non-smoker), regular exercise (dichotomous; taking regular exercise of more than 30 minutes per day for more than one year or not), and body mass index (BMI) (categorical; quartile). BMI was defined as body weight (kg) divided by height squared (m^2). All individual variables were obtained at the baseline health checkup and the variables other than BMI were self-reported.

We then estimated the HRs from stratified analyses by age category (< 75 or ≥ 75 years) and sex (male or female). In the sensitivity analyses, we added current disease status (hyperlipidemia, heart disease, and others [i.e., renal disease, liver disease, and anemia]) in order, as potential confounders to the fully adjusted model. We also excluded participants with less than 24 follow-up months in the fully adjusted model, to consider the possibility of reverse causation.

We calculated all confidence intervals (CIs) at the 95% level, and a value of $p < 0.05$ was considered statistically significant. We used Stata SE version 17 (StataCorp, College Station, TX, USA) for all analyses. The study was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital (No. K2106-038).

3. Results

3.1. Descriptive analysis

Table 1 shows the baseline characteristics by frailty group. Among the 43,312 participants, the mean age was 75.3 years and 64% were women. Mean follow-up time

was 9.3 years (range 3–129 months). The prevalence was 28.8% (n = 12,470) for prefrailty and 29.7% (n = 12,867) for frailty. Compared with the participants in the robust group, those in the prefrail and frail groups tended to be older, women, take less regular exercise, and have more comorbidities. The participants who died during the follow-up tended to be older and current smokers (Supplementary Table 2).

3.2. Survival analysis

The Kaplan–Meier curves of survival probability for participants during follow-up suggested that the participants who were frail at baseline had the lowest survival probabilities compared with those who were robust or prefrail (Figure 2). The difference in rates of death from cancer between frail and prefrail individuals was smaller than for other causes, although still statistically significantly different. We show the HRs in Table 2. Compared to the robust group, the prefrail and the frail groups had an increased risk of all-cause and cause-specific mortality. The fully adjusted HR for all-cause mortality was 1.34 (95% CI: 1.27- 1.41) for the prefrail group and 2.22 (95% CI: 2.11-2.33) for the frail group. The HRs and 95% CIs for the prefrail and frail groups for causespecific mortality were 1.35 (95% CI: 1.21-1.51) and 2.55 (95% CI: 2.30-2.82) for CVD mortality, 1.63 (95% CI: 1.43-1.86) and 2.99 (95% CI: 2.64-3.39) for respiratory disease mortality, and 1.23 (95% CI: 1.12- 1.34) and 1.39 (95% CI: 1.26-1.53) for cancer mortality. A similar pattern was also seen for each cause when we examined more specific causes of death (Supplementary Table 3). However, frailty was more strongly associated with CVD and respiratory disease mortality than with cancer mortality.

3.3. Stratified analysis and Sensitivity analysis

In the stratified analysis by age and sex (Table 3), younger people and women tended to show higher effect estimates, but the elevated risks were seen in all strata. In the sensitivity analyses, the point estimates of HRs did not change substantially (Supplementary Tables 4 and 5).

4. Discussion

In this study, we evaluated the association between frailty, assessed using KCL scores, and all-cause and cause-specific mortality, over a long follow-up period in Japan. We found that frailty and prefrailty were associated with an increased risk of all-cause and cause-specific mortality (i.e., CVD, respiratory disease, and cancer mortality). Younger group (65–74 years) and women tended to have higher effect estimates than older group (≥ 75 years) and men.

Frailty is often assessed by either frailty index or frailty phenotype. Frailty index can be flexibly constructed based on an arbitrary set of deficits such as symptoms, signs, disabilities, and disease. However, previous studies have mainly constructed it from the presence of disease (Fan et al., 2020; Jiang et al., 2017; Li et al., 2019; Williams et al., 2019). It would probably be more informative to focus on the effect of functional assessment of frailty on health outcomes, rather than the effect of the presence of disease. On the other hand, there is limited evidence for an association between frailty phenotype, which assesses frailty using functions and signs, and subsequent cause-specific mortality. We therefore used the KCL to evaluate frailty, which is similar to the frailty phenotype.

Our findings on all-cause mortality are consistent with the previous study that used the KCL scale to assess frailty. It found an elevated risk for 3-year mortality among the frailty group (≥ 8 points on the scale) than the robust group (0–3 points).

However, there was no elevated risk among prefrail participants (4–7 points) (Satake et al., 2017). Our study provides further evidence on this issue by extending the follow-up period to 10 years. We found that even the prefrail group had a higher risk of all-cause mortality over this length of time than the robust group. Our findings suggest that it is important to identify both frailty and prefrailty to avoid adverse health outcomes and enable early intervention to prevent the transition from prefrail to frail.

Most of the evidence for the association of frailty with increased risk of CVD and respiratory disease came from studies that used the frailty index for frailty assessment (Fan et al., 2020; Jiang et al., 2017; Li et al., 2019). However, a limited number of studies assessed the association of frailty phenotype with CVD and respiratory disease mortality. For example, a recent study from the United States used frailty phenotype and found that frailty was associated with heart disease and respiratory disease mortality. Our results are consistent with these findings (Lohman et al., 2020). These results suggest that we should focus on the prevention and management of CVD and respiratory disease especially among frail older people.

The effect estimates were lower for cancer than CVD and respiratory disease mortality, but we still found that prefrailty and frailty assessed by the KCL were associated with cancer mortality. Previous studies that evaluated the association between cancer mortality and frailty provided conflicting evidence. Some reports from the United States and China (Fan et al., 2020; Lohman et al., 2020) found positive associations, but others from Sweden (Jiang et al., 2017; Li et al., 2019) did not. Our study provides further evidence from a long-term follow-up. One systematic review (Handforth et al., 2015) demonstrated that frail and prefrail older people were at considerably increased risk of postoperative mortality or complications as well as chemotherapy intolerance. This review also suggested that older cancer patients had a

higher prevalence of frailty. These findings indicate that frailty and cancer may synergistically worsen the health status of older people.

Younger group (65–74 years) had higher effect estimates than the older group (≥ 75 years) in our study, which is also consistent with previous findings (Fan et al., 2020; Jiang et al., 2017). This shows that the frailty status at the ages of 65–74 years is more related to subsequent adverse health outcomes than frailty at ≥ 75 years. The prevalence of frailty is not rare among middle-aged people (Santos-Eggimann et al., 2009), and we should therefore be able to support both frail middle-aged and older people. The evidence from a life-course approach shows that the presence of behavioral and biomedical risk factors in midlife is associated with frailty in later life (Lafortune et al., 2016; Stenholm et al., 2014; Szanton et al., 2009). It is therefore also important to manage these risk factors for frailty.

We found that women had higher effect estimates than men, which may be explained by the male–female health–survival paradox. The paradox means that women live longer than men on average despite suffering a higher burden of comorbidity (Gordon et al., 2017). In both this and previous studies, the prevalence of frailty was higher in women than men (Bandein-Roche et al., 2015; Santos-Eggimann et al., 2009), but women lived longer. This may indicate that men die because of other causes, but the cause of death among women is more closely related to frailty. It may therefore be effective to consider strategies that manage frailty among women. However, further studies are warranted to evaluate the sex differences in the impact of frailty.

Finally, the KCL has two strengths as a frailty screening tool. First, it uses self-reported questionnaires and does not require special equipment. It is therefore easier and quicker to implement than the frailty index or frailty phenotype (Cesari et al., 2014; Dent et al., 2016; Kojima et al., 2018). Second, the KCL differs from the frailty

phenotype because it assesses physical, psychological (i.e., cognitive function and depressive mood) and social frailty (i.e., homebound status and social isolation). This may help to identify the specific causes of frailty and provide more focused interventions for frail people (Satake et al., 2019). To improve the assessment of frailty, it will be important to reflect those beneficial characteristics of the KCL in any future studies.

Our study has several strengths. First, we could identify the survival status of most of the participants, and selection bias by follow-up status would therefore be small. Second, demographic characteristics obtained from the baseline questionnaire enabled us to adjust for a wide range of potential confounders. However, the study also had several limitations. First, there is a possibility of exposure misclassification because of the self-reporting, but this misclassification would be non-differential, and the true effects would be biased toward the null. Moreover, the KCL was already well validated with the frailty phenotype and the frailty index, respectively (Kojima et al., 2018; Satake et al., 2016). Second, we excluded participants who did not complete the KCL and the proportion of mortality of this group was higher than in the group that completed the KCL (34.6% vs 28.0%). This selection bias may therefore have underestimated the effect estimates. Third, residual confounding was still possible because we could not adjust for individual-level socioeconomic variables and cognitive functions. Finally, the prevalence of frailty may vary depending on the definition of frailty, especially assessed by the frailty index, and depending on the participants of the studies (Abete et al., 2017; Fan et al., 2020). This study used a cohort of health checkup participants. Compared to the population distribution by age group and sex from the 2005 census of Okayama City, the study population of the present study was older and had a higher proportion of women. Moreover, they are more health-conscious compared

to general population; thus, the results (i.e., the prevalence and the effect estimates) should therefore be generalized with caution.

5. Conclusion and implications

This study showed that prefrailty and frailty can increase the risk of all-cause and cause-specific mortality over a long-term follow-up period in Japan, the most aged country in the world. Our study suggests that to support frail people, it could be effective to focus on the prevention and management of CVD and respiratory disease. It also suggests that the KCL may be useful as a method of screening for frailty.

Author contributions

R Matsuo: Conceptualization, Methodology, Formal analysis, Writing- Original draft preparation. T Mitsuhashi: Methodology, Validation, Formal analysis. N Matsumoto and S Takao: Conceptualization, Writing - Review & Editing. T Yorifuji: Conceptualization, Funding acquisition, Writing - Review & Editing, Supervision.

All authors read and approved the final manuscript.

Funding

This work was supported by JSPS KAKENHI Grant Number (C) 20K10471. The sponsors have had no involvement in the study design, the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit the paper for publication.

Conflicts of Interest

None declared.

Acknowledgments

We thank Hiroaki Matsuoka, Saori Irie, and Yoko Oka for valuable support in collecting data. We also thank Melissa Leffler, MBA, from Edanz (<https://jp.edanz.com/ac>) for editing a draft of this manuscript.

References

- Abete, P., Basile, C., Bulli, G., Curcio, F., Liguori, I., Della-Morte, D., Gargiulo, G., Langellotto, A., Testa, G., Galizia, G., Bonaduce, D., Cacciatore, F., 2017. The Italian version of the "frailty index" based on deficits in health: a validation study. *Aging Clin Exp Res* 29, 913-926.
- Akishita, M., Suzuki, S., Inoue, H., Akao, M., Atarashi, H., Ikeda, T., Koretsune, Y., Okumura, K., Shimizu, W., Tsutsui, H., Toyoda, K., Hirayama, A., Yasaka, M., Yamaguchi, T., Teramukai, S., Kimura, T., Morishima, Y., Takita, A., Yamashita, T., 2022. Frailty and outcomes in older adults with non-valvular atrial fibrillation from the ANAFIE registry. *Arch Gerontol Geriatr* 101, 104661.
- Bandeem-Roche, K., Seplaki, C.L., Huang, J., Buta, B., Kalyani, R.R., Varadhan, R., Xue, Q.L., Walston, J.D., Kasper, J.D., 2015. Frailty in Older Adults: A Nationally Representative Profile in the United States. *J Gerontol A Biol Sci Med Sci* 70, 1427-1434.
- Cesari, M., Gambassi, G., van Kan, G.A., Vellas, B., 2014. The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing* 43, 10-12.
- Clegg, A., Young, J., Iliffe, S., Rikkert, M.O., Rockwood, K., 2013. Frailty in elderly people. *The Lancet* 381, 752-762.
- Dent, E., Kowal, P., Hoogendijk, E.O., 2016. Frailty measurement in research and clinical practice: A review. *Eur J Intern Med* 31, 3-10.
- Fan, J., Yu, C., Guo, Y., Bian, Z., Sun, Z., Yang, L., Chen, Y., Du, H., Li, Z., Lei, Y., Sun, D., Clarke, R., Chen, J., Chen, Z., Lv, J., Li, L., 2020. Frailty index and all-cause and cause-specific mortality in Chinese adults: a prospective cohort study. *Lancet Public Health* 5, e650-e660.
- Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J.,

- Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., 2001. Frailty in Older Adults: Evidence for a Phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 56, M146-M157.
- Gordon, E.H., Peel, N.M., Samanta, M., Theou, O., Howlett, S.E., Hubbard, R.E., 2017. Sex differences in frailty: A systematic review and meta-analysis. *Experimental Gerontology* 89, 30-40.
- Handforth, C., Clegg, A., Young, C., Simpkins, S., Seymour, M.T., Selby, P.J., Young, J., 2015. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol* 26, 1091-1101.
- Hoogendijk, E.O., Afilalo, J., Ensrud, K.E., Kowal, P., Onder, G., Fried, L.P., 2019. Frailty: implications for clinical practice and public health. *The Lancet* 394, 1365-1375.
- Jiang, M., Foebel, A.D., Kuja-Halkola, R., Karlsson, I., Pedersen, N.L., Hägg, S., Jylhävä, J., 2017. Frailty index as a predictor of all-cause and cause-specific mortality in a Swedish population-based cohort. *Aging (Albany NY)* 9, 2629-2646.
- Kojima, G., Taniguchi, Y., Kitamura, A., Shinkai, S., 2018. Are the Kihon Checklist and the Kaigo-Yobo Checklist Compatible With the Frailty Index? *J Am Med Dir Assoc* 19, 797-800.e792.
- Lafortune, L., Martin, S., Kelly, S., Kuhn, I., Remes, O., Cowan, A., Brayne, C., 2016. Behavioural Risk Factors in Mid-Life Associated with Successful Ageing, Disability, Dementia and Frailty in Later Life: A Rapid Systematic Review. *PLoS One* 11, e0144405.
- Li, X., Ploner, A., Karlsson, I.K., Liu, X., Magnusson, P.K.E., Pedersen, N.L., Hägg, S., Jylhävä, J., 2019. The frailty index is a predictor of cause-specific mortality independent of familial effects from midlife onwards: a large cohort study. *BMC Medicine* 17.
- Lohman, M.C., Sonnegä, A.J., Resciniti, N.V., Leggett, A.N., 2020. Frailty Phenotype

and Cause-Specific Mortality in the United States. *J Gerontol A Biol Sci Med Sci* 75, 1935-1942.

Okayama Prefecture, 2013. [Basic health checkups] (in Japanese).

Rockwood, K., Mitnitski, A., 2007. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci* 62, 722-727.

Santos-Eggimann, B., Cuenoud, P., Spagnoli, J., Junod, J., 2009. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *J Gerontol A Biol Sci Med Sci* 64, 675-681.

Satake, S., Senda, K., Hong, Y.J., Miura, H., Endo, H., Sakurai, T., Kondo, I., Toba, K., 2016. Validity of the Kihon Checklist for assessing frailty status. *Geriatr Gerontol Int* 16, 709-715.

Satake, S., Shimokata, H., Senda, K., Kondo, I., Arai, H., Toba, K., 2019. Predictive Ability of Seven Domains of the Kihon Checklist for Incident Dependency and Mortality. *J Frailty Aging* 8, 85-87.

Satake, S., Shimokata, H., Senda, K., Kondo, I., Toba, K., 2017. Validity of Total Kihon Checklist Score for Predicting the Incidence of 3-Year Dependency and Mortality in a Community-Dwelling Older Population. *J Am Med Dir Assoc* 18, 552.e551-552.e556.

Searle, S.D., Mitnitski, A., Gahbauer, E.A., Gill, T.M., Rockwood, K., 2008. A standard procedure for creating a frailty index. *BMC Geriatr* 8, 24.

Sewo Sampaio, P.Y., Sampaio, R.A., Yamada, M., Arai, H., 2016. Systematic review of the Kihon Checklist: Is it a reliable assessment of frailty? *Geriatr Gerontol Int* 16, 893-902.

Stenholm, S., Strandberg, T.E., Pitkala, K., Sainio, P., Heliovaara, M., Koskinen, S., 2014. Midlife obesity and risk of frailty in old age during a 22-year follow-up in men and women: the Mini-Finland Follow-up Survey. *J Gerontol A Biol Sci Med Sci* 69, 73-

78.

Szanton, S.L., Allen, J.K., Seplaki, C.L., Bandeen-Roche, K., Fried, L.P., 2009.

Allostatic load and frailty in the women's health and aging studies. *Biol Res Nurs* 10, 248-256.

Veronese, N., Cereda, E., Stubbs, B., Solmi, M., Luchini, C., Manzato, E., Sergi, G., Manu, P., Harris, T., Fontana, L., Strandberg, T., Amieva, H., Dumurgier, J., Elbaz, A., Tzourio, C., Eicholzer, M., Rohrmann, S., Moretti, C., D'Ascenzo, F., Quadri, G., Polidoro, A., Lourenço, R.A., Moreira, V.G., Sanchis, J., Scotti, V., Maggi, S., Correll, C.U., 2017. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: Results from a meta-analysis and exploratory meta-regression analysis. *Ageing Res Rev* 35, 63-73.

Walston, J.D., Bandeen-Roche, K., 2015. Frailty: a tale of two concepts. *BMC Med* 13, 185.

Williams, D.M., Jylhävä, J., Pedersen, N.L., Hägg, S., 2019. A Frailty Index for UK Biobank Participants. *J Gerontol A Biol Sci Med Sci* 74, 582-587.

Table 1

Demographic characteristics of study participants by frailty status (n=43,312)

	Total (n=43,312)	robust (n=17,975)	prefrail (n=12,470)	frail (n=12,867)
Mean age (year) $\pm$ SD	75.3 $\pm$ 6.7	72.6 $\pm$ 5.3	74.8 $\pm$ 5.8	79.6 $\pm$ 7.0
Sex, women, n (%)	27719 (64.0)	10634 (59.2)	8086 (64.8)	8999 (69.9)
Examination year, in 2006, n (%)	34707 (80.1)	14557 (81.0)	10052 (80.6)	10098 (78.5)
Mean body mass index $\pm$ SD	22.9 $\pm$ 3.4	23.1 $\pm$ 3.0	23.0 $\pm$ 3.0	22.4 $\pm$ 3.8
Regular exercise, n (%)	19186 (45.4)	9793 (55.6)	5483 (45.1)	3910 (31.2)
Alcohol Consumption, n (%)	13080 (30.8)	6753 (38.2)	3818 (31.2)	2509 (19.9)
Current smoking, n (%)	3954 (9.2)	1626 (9.1)	1216 (9.8)	1112 (8.7)
Hypertension, n (%)	18136 (41.9)	6932 (38.6)	5302 (42.5)	5902 (45.9)
Diabetes, n (%)	4141 (9.6)	1483 (8.3)	1158 (9.3)	1500 (11.7)

Subjects with missing data was excluded from the analysis.

There were 15 cases missing on body mass index, 1017 cases missing on regular exercise, 778 cases missing on alcohol consumption, and 396 cases missing on smoking status.

SD, standard deviation.

Table 2

Crude and adjusted HRs and 95% confidence intervals for all-cause and cause-specific mortality by frailty status (n=43,312)

	case / Total n / N (%)	crude HR (95% CI)	Age and sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)*
All-cause mortality	12,136			
robust	2697 / 17975 (15.0)	1.0 (reference)	1.0 (reference)	1.0 (reference)
prefrail	2979 / 12470 (23.9)	1.69 (1.60 - 1.78)	1.39 (1.32 - 1.47)	1.34 (1.27 - 1.41)
frail	6460 / 12867 (50.2)	4.49 (4.29 - 4.70)	2.45 (2.34 - 2.58)	2.22 (2.11 - 2.33)
Cause-specific mortality				
Cardiovascular disease (I00-I99)	3,429			
robust	643 / 17975 (3.6)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	760 / 12470 (6.1)	1.80 (1.62 - 2.00)	1.43 (1.28 - 1.59)	1.35 (1.21 - 1.51)
frail	2026 / 12867 (15.7)	5.87 (5.37 - 6.41)	2.87 (2.61 - 3.16)	2.55 (2.30 - 2.82)
Respiratory disease (J00-J99)	2,309			
robust	420 / 17975 (2.3)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	546 / 12470 (4.4)	1.98 (1.75 - 2.25)	1.67 (1.47 - 1.89)	1.63 (1.43 - 1.86)
frail	1343 / 12867 (10.4)	6.02 (5.39 - 6.71)	3.35 (2.98 - 3.78)	2.99 (2.64 - 3.39)
Cancer (C00-C97)	3,176			
robust	1053 / 17975 (5.9)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	962 / 12470 (7.7)	1.39 (1.27 - 1.52)	1.27 (1.17 - 1.39)	1.23 (1.12 - 1.34)
frail	1161 / 12867 (9.0)	2.03 (1.87 - 2.21)	1.49 (1.36 - 1.63)	1.39 (1.26 - 1.53)

* Adjusted for age, sex, hypertension, diabetes, alcohol drinking, smoking status, regular exercise, and body mass index.

CI, confidence interval; HR, hazard ratio.

Table 3

Stratified analysis by age and sex: Adjusted HRs* for all-cause and cause-specific mortality by frailty status (n=43,312)

	case / Total n / N (%)	robust (reference)	prefrail HR (95% CI)	frail HR (95% CI)
All-cause mortality				
age				
65-74	2573 / 21690 (11.9)	1.0 (ref)	1.50 (1.36 - 1.65)	3.03 (2.75 - 3.34)
≥ 75	9563 / 21622 (44.2)	1.0 (ref)	1.38 (1.29 - 1.47)	2.89 (2.72 - 3.06)
sex				
women	6441 / 27719 (23.2)	1.0 (ref)	1.34 (1.23 - 1.46)	2.27 (2.10 - 2.45)
men	5695 / 15593 (36.5)	1.0 (ref)	1.35 (1.26 - 1.45)	2.15 (2.01 - 2.31)
Cause-specific mortality				
Cardiovascular disease (I00-I99)				
age				
65-74	606 / 21690 (2.8)	1.0 (ref)	1.79 (1.45 - 2.20)	4.37 (3.56 - 5.35)
≥ 75	2823 / 21622 (13.1)	1.0 (ref)	1.31 (1.15 - 1.48)	3.20 (2.87 - 3.57)
sex				
women	2022 / 27719 (7.3)	1.0 (ref)	1.39 (1.18 - 1.63)	2.59 (2.24 - 3.00)
men	1407 / 15593 (9.0)	1.0 (ref)	1.33 (1.14 - 1.55)	2.49 (2.16 - 2.86)
Respiratory disease (J00-J99)				
age				
65-74	364 / 21690 (1.7)	1.0 (ref)	1.59 (1.22 - 2.08)	4.14 (3.21 - 5.35)
≥ 75	1945 / 21622 (9.0)	1.0 (ref)	1.75 (1.51 - 2.04)	3.93 (3.43 - 4.50)
sex				
women	961 / 27719 (3.5)	1.0 (ref)	1.92 (1.49 - 2.47)	3.57 (2.82 - 4.53)
men	1348 / 15593 (8.6)	1.0 (ref)	1.55 (1.32 - 1.81)	2.78 (2.40 - 3.22)
Cancer (C00-C97)				
age				
65-74	1036 / 21690 (4.8)	1.0 (ref)	1.35 (1.17 - 1.56)	1.92 (1.63 - 2.27)
≥ 75	2140 / 21622 (9.9)	1.0 (ref)	1.20 (1.07 - 1.35)	1.50 (1.34 - 1.68)
sex				
women	1456 / 27719 (5.3)	1.0 (ref)	1.26 (1.09 - 1.46)	1.43 (1.24 - 1.66)
men	1720 / 15593 (11.0)	1.0 (ref)	1.20 (1.07 - 1.35)	1.33 (1.17 - 1.51)

* Adjusted for age, sex, hypertension, diabetes, alcohol drinking, smoking status, regular exercise, and body mass index.

CI, confidence interval; HR, hazard ratio.

Figure legends

Figure 1. A flow chart of participants.

Figure 2. Kaplan–Meier survival probabilities by frailty status.

All p-values for the log-rank test comparing survival distributions of the three frailty status groups were < 0.0001 .

Figure 1.

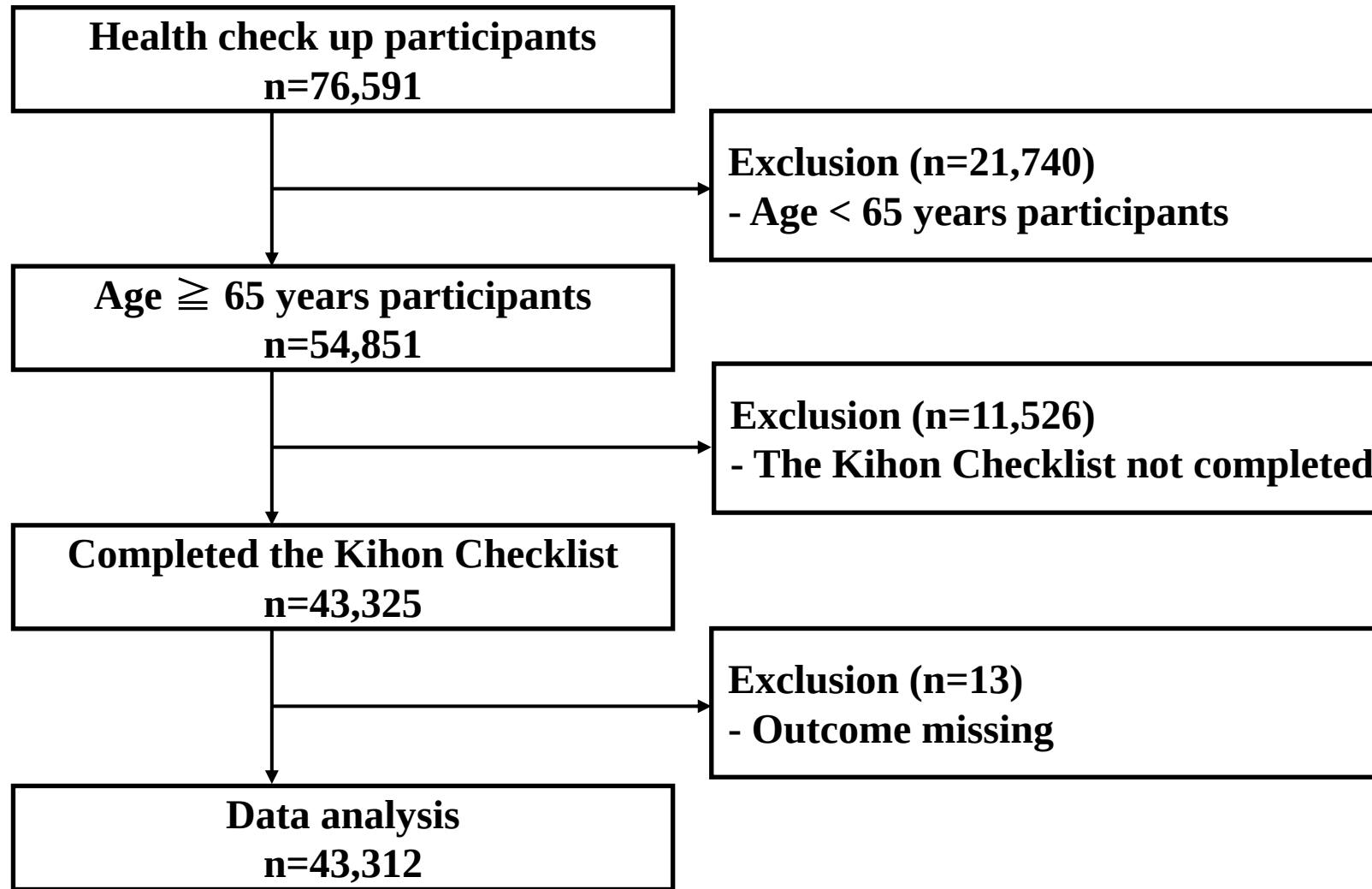
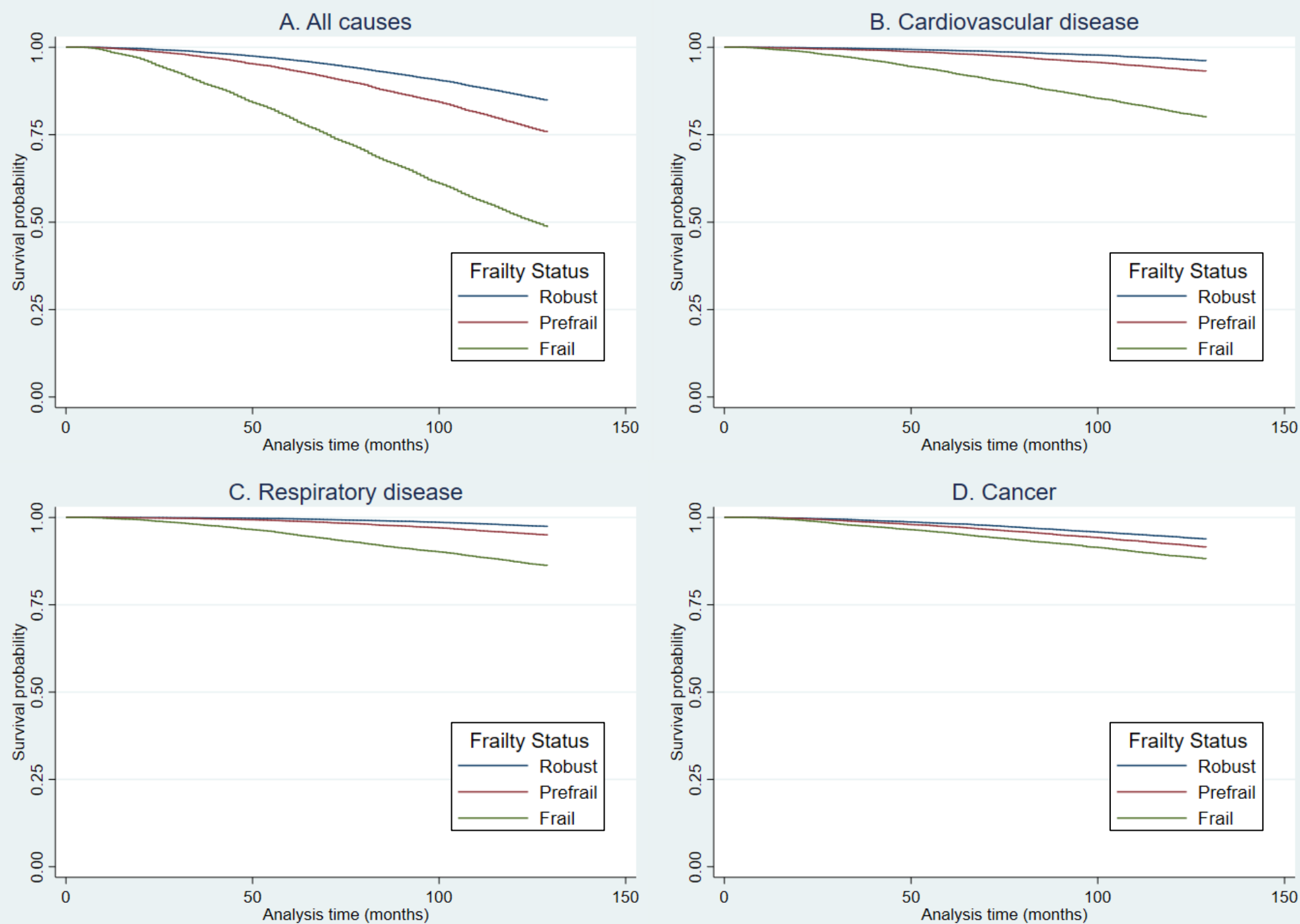


Figure2



Original research Article

Frailty and all-cause and cause-specific mortality in Japan

Supplementary materials

Supplementary Table 1. Kihon Checklist

Supplementary Table 2. Demographic characteristics of study participants by follow up status
(n=43,312)

Supplementary Table 3. Crude and adjusted HRs for specific-cause mortality by frailty status
(n=43,312)

Supplementary Table 4. Sensitivity analysis adjusted for other possible confounders

Supplementary Table 5. Sensitivity analysis that excluded participants with follow-up months less than 24 months (n=42,183)

Supplementary Table1

Kihon Checklist

No.	Questions	Answer	
1	Do you go out by bus or train by yourself?	0. YES	1. NO
2	Do you go shopping to buy daily necessities by yourself?	0. YES	1. NO
3	Do you manage your own deposits and savings at the bank?	0. YES	1. NO
4	Do you sometimes visit your friends?	0. YES	1. NO
5	Do you turn to your family or friends for advice?	0. YES	1. NO
6	Do you normally climb stairs without using handrail or wall for support?	0. YES	1. NO
7	Do you normally stand up from a chair without any aids?	0. YES	1. NO
8	Do you normally walk continuously for 15 min?	0. YES	1. NO
9	Have you experienced a fall in the past year?	1. YES	0. NO
10	Do you have a fear of falling while walking?	1. YES	0. NO
11	Have you lost 2 kg or more in the past 6 months?	1. YES	0. NO
12	Height: cm, weight: kg, BMI: kg/m ² If BMI is less than 18.5, this item is scored.	1. YES	0. NO
13	Do you have any difficulties eating tough foods compared to 6 months ago?	1. YES	0. NO
14	Have you choked on your tea or soup recently?	1. YES	0. NO
15	Do you often experience having a dry mouth?	1. YES	0. NO
16	Do you go out at least once a week?	0. YES	1. NO
17	Do you go out less frequently compared to last year?	1. YES	0. NO
18	Do your family or your friends point out your memory loss? e.g. "You ask the same question."	1. YES	0. NO
19	Do you make a call by looking up phone numbers?	0. YES	1. NO
20	Do you find yourself not knowing today's date?	1. YES	0. NO
21	In the last 2 weeks have you felt a lack of fulfilment in your daily life?	1. YES	0. NO
22	In the last 2 weeks have you felt a lack of joy when doing the things you used to enjoy?	1. YES	0. NO
23	In the last 2 weeks have you felt difficulty in doing what you could do easily before?	1. YES	0. NO
24	In the last 2 weeks have you felt helpless?	1. YES	0. NO
25	In the last 2 weeks have you felt tired without a reason?	1. YES	0. NO

BMI, body mass index.

Supplementary Table 2

Demographic characteristics of study participants by follow up status (n=43,312)

	Total (n=43,312)	survive at study end (n=29,922)	lost to follow-up (n=1,254)	died (n=12,136)
Mean age (year) $\pm$ SD	75.3 $\pm$ 6.7	76.8 $\pm$ 6.5	74.8 $\pm$ 5.8	80.3 $\pm$ 6.9
Sex, women, n (%)	27719 (64.0)	20346 (68.0)	932 (74.3)	6441 (53.1)
Examination year, in 2006, n (%)	34707 (80.1)	23916 (79.9)	1044 (83.3)	9747 (80.3)
Mean body mass index $\pm$ SD	22.9 $\pm$ 3.4	22.7 $\pm$ 3.5	23.0 $\pm$ 3.4	22.0 $\pm$ 3.6
Regular exercise, n (%)	19186 (45.4)	14283 (48.8)	562 (45.6)	4341 (36.7)
Alcohol Consumption, n (%)	13080 (30.8)	9536 (32.4)	320 (26.0)	3224 (27.1)
Current smoking, n (%)	3954 (9.2)	2334 (7.9)	90 (7.2)	1530 (12.7)
Hypertension, n (%)	18136 (41.9)	12019 (40.2)	503 (40.1)	5614 (46.3)
Diabetes, n (%)	4141 (9.6)	2462 (8.2)	124 (9.9)	1555 (12.8)

Subjects with missing data was excluded from the analysis.

There were 15 cases missing on body mass index, 1017 cases missing on regular exercise, 778 cases missing on alcohol consumption, and 396 cases missing on smoking status.

SD, standard deviation.

Supplementary Table 3

Crude and adjusted HRs* for specific-cause mortality by frailty status (n=43,312)

	case / Total n / N (%)	crude HR (95% CI)	Age and sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)*
Cardiovascular disease				
Ischemic heart disease	699			
robust	156 / 17975 (0.9)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	178 / 12470 (1.4)	1.74 (1.40 - 2.16)	1.46 (1.18 - 1.82)	1.45 (1.15 - 1.81)
frail	365 / 12867 (2.8)	4.35 (3.61 - 5.25)	2.50 (2.03 - 3.07)	2.32 (1.87 - 2.88)
Heart failure	822			
robust	126 / 17975 (0.7)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	180 / 12470 (1.4)	2.18 (1.73 - 2.73)	1.58 (1.26 - 1.99)	1.53 (1.20 - 1.93)
frail	516 / 12867 (4.0)	7.62 (6.27 - 9.26)	2.91 (2.36 - 3.60)	2.68 (2.15 - 3.35)
Cerebrovascular disease	1,205			
robust	224 / 17975 (1.2)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	238 / 12470 (1.9)	1.62 (1.35 - 1.94)	1.34 (1.12 - 1.61)	1.20 (0.99 - 1.45)
frail	743 / 12867 (5.8)	6.14 (5.29 - 7.14)	3.41 (2.90 - 4.02)	2.87 (2.43 - 3.40)
Respiratory disease				
Pneumonia (include influenza)	1,352			
robust	219 / 17975 (1.2)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	294 / 12470 (2.4)	2.05 (1.72 - 2.44)	1.68 (1.41 - 2.00)	1.67 (1.39 - 2.01)
frail	839 / 12867 (6.5)	7.19 (6.19 - 8.34)	3.74 (3.19 - 4.39)	3.44 (2.91 - 4.07)
Aspiration pneumonia	411			

robust	70 / 17975 (0.4)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	101 / 12470 (0.8)	2.21 (1.63 - 3.00)	1.82 (1.34 - 2.47)	1.77 (1.30 - 2.42)
frail	240 / 12867 (1.9)	6.61 (5.06 - 8.63)	3.46 (2.60 - 4.61)	2.93 (2.18 - 3.94)
Cancer				
Lung cancer	656			
robust	219 / 17975 (1.2)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	190 / 12470 (1.5)	1.32 (1.09 - 1.60)	1.26 (1.03 - 1.53)	1.16 (0.95 - 1.42)
frail	247 / 12867 (1.9)	2.07 (1.73 - 2.49)	1.66 (1.36 - 2.03)	1.48 (1.21 - 1.83)
Colon cancer	259			
robust	65 / 17975 (0.4)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	70 / 12470 (0.6)	1.65 (1.17 - 2.31)	1.37 (0.97 - 1.93)	1.34 (0.95 - 1.89)
frail	124 / 12867 (1.0)	3.60 (2.67 - 4.87)	2.04 (1.46 - 2.85)	1.92 (1.37 - 2.70)
Gastric cancer	398			
robust	134 / 17975 (0.7)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	119 / 12470 (1.0)	1.34 (1.05 - 1.72)	1.21 (0.94 - 1.56)	1.21 (0.94 - 1.57)
frail	145 / 12867 (1.1)	1.96 (1.55 - 2.48)	1.36 (1.05 - 1.76)	1.34 (1.02 - 1.76)

* Adjusted for age, sex, hypertension, diabetes, alcohol drinking, smoking status, regular exercise, and body mass index.

CI, confidence interval; HR, hazard ratio.

Supplementary Table 4

Sensitivity analysis adjusted for other possible confounders

	case / Total n / N (%)	model1 † HR (95% CI)	model2 ‡ HR (95% CI)	model3 § HR (95% CI)
All-cause mortality				
robust	2697 / 17975 (15.0)	1.0 (reference)	1.0 (reference)	1.0 (reference)
prefrail	2979 / 12470 (23.9)	1.34 (1.27 - 1.41)	1.33 (1.26 - 1.41)	1.32 (1.25 - 1.40)
frail	6460 / 12867 (50.2)	2.20 (2.09 - 2.32)	2.18 (2.07 - 2.30)	2.15 (2.04 - 2.26)
Cause-specific mortality				
Cardiovascular disease (I00-I99)				
robust	643 / 17975 (3.6)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	760 / 12470 (6.1)	1.35 (1.21 - 1.51)	1.34 (1.20 - 1.49)	1.33 (1.20 - 1.49)
frail	2026 / 12867 (15.7)	2.53 (2.29 - 2.80)	2.47 (2.23 - 2.73)	2.45 (2.22 - 2.71)
Respiratory disease (J00-J99)				
robust	420 / 17975 (2.3)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	546 / 12470 (4.4)	1.63 (1.43 - 1.86)	1.63 (1.43 - 1.86)	1.63 (1.42 - 1.85)
frail	1343 / 12867 (10.4)	2.98 (2.63 - 3.37)	2.95 (2.61 - 3.34)	2.93 (2.59 - 3.31)
Cancer (C00-C97)				
robust	1053 / 17975 (5.9)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	962 / 12470 (7.7)	1.23 (1.12 - 1.34)	1.23 (1.12 - 1.34)	1.21 (1.11 - 1.33)
frail	1161 / 12867 (9.0)	1.38 (1.26 - 1.52)	1.38 (1.26 - 1.52)	1.35 (1.23 - 1.49)

* Fully adjusted model: Adjusted for age, sex, hypertension, diabetes, alcohol drinking, smoking status, regular exercise, and body mass index.

† model1: Fully adjusted model*+ hyperlipidemia

‡ model2: model1 + heart disease

§ model3: model2 + renal disease, liver disease and anemia

CI, confidence interval; HR, hazard ratio.

Supplementary Table 5

Sensitivity analysis that excluded participants with follow-up months less than 24 months (n=42,183)

	case / Total n / N (%)	crude HR (95% CI)	Age and sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)*
All-cause mortality	11,203			
robust	2579 / 17794 (14.5)	1.0 (reference)	1.0 (reference)	1.0 (reference)
prefrail	2818 / 12269 (23.0)	1.67 (1.59 - 1.77)	1.39 (1.31 - 1.46)	1.33 (1.26 - 1.41)
frail	5806 / 12120 (47.9)	4.31 (4.12 - 4.52)	2.39 (2.27 - 2.51)	2.17 (2.06 - 2.29)
Cause-specific mortality				
Cardiovascular disease (I00-I99)	3,126			
robust	613 / 17794 (3.4)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	705 / 12269 (5.7)	1.76 (1.58 - 1.96)	1.40 (1.25 - 1.56)	1.33 (1.19 - 1.49)
frail	1808 / 12120 (14.9)	5.63 (5.13 - 6.17)	2.78 (2.52 - 3.08)	2.49 (2.25 - 2.77)
Respiratory disease (J00-J99)	2,151			
robust	415 / 17794 (2.3)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	529 / 12269 (4.3)	1.95 (1.72 - 2.22)	1.65 (1.45 - 1.87)	1.62 (1.42 - 1.85)
frail	1207 / 12120 (10.0)	5.58 (4.99 - 6.24)	3.17 (2.81 - 3.57)	2.87 (2.53 - 3.25)
Cancer (C00-C97)	3,176			
robust	992 / 17794 (5.6)	1.0 (ref)	1.0 (ref)	1.0 (ref)
prefrail	900 / 12269 (7.3)	1.38 (1.27 - 1.52)	1.28 (1.16 - 1.40)	1.23 (1.12 - 1.35)
frail	1019 / 12120 (8.4)	1.94 (1.77 - 2.11)	1.44 (1.31 - 1.59)	1.35 (1.22 - 1.49)

* Adjusted for age, sex, hypertension, diabetes, alcohol drinking, smoking status, regular exercise, and body mass index.

CI, confidence interval; HR, hazard ratio.