Original Contribution

Trends in Frailty and Its Association With Mortality: Results From the Longitudinal Aging Study Amsterdam, 1995–2016

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The aim of this study was to investigate trends in frailty and its relationship with mortality among older adults aged 64–84 years across a period of 21 years. We used data from 1995 to 2016 from the Longitudinal Aging Study Amsterdam. A total of 7,742 observations of 2,874 respondents in the same age range (64–84 years) across 6 measurement waves were included. Frailty was measured with a 32-item frailty index, with a cutpoint of ≥0.25 to indicate frailty. The outcome measure was 4-year mortality. Generalized estimating equation analyses showed that among older adults aged 64–84 years the 4-year mortality rate declined between 1995 and 2016, while the prevalence of frailty increased. Across all measurement waves, frailty was associated with 4-year mortality (odds ratio = 2.79, 95% confidence interval: 2.39, 3.26). There was no statistically significant interaction effect between frailty and time on 4-year mortality, indicating a stable association between frailty and mortality. In more recent generations of older adults, frailty prevalence rates were higher, while excess mortality rates of frailty remained the same. This is important information for health policy-makers and clinical practitioners, showing that continued efforts are needed to reduce frailty and its negative health consequences.

cohort study; frailty index; frail older adults; mortality

In aging societies, the concept of frailty has gained increased attention (1). Frailty in older adults is defined as a decrease in reserve capacity in multiple physiological systems and elevated vulnerability to stressors (2). It is associated with greater health-care utilization and various adverse outcomes (1). For instance, frailty is one of the most important contributors to mortality in later life (3, 4).

In recent decades, life expectancy has increased in most developed countries, and this also applies to the life expectancy at age 65 (5). It has been suggested that this positive trend in life expectancy is the result of better living circumstances and improved medical care (5). For example, premature mortality from chronic diseases such as diabetes and cardiovascular disease has declined due to better medical treatment (6, 7). However, at the same time, some studies have indicated that the increase in life expectancy in older adults is accompanied by more years spent in poor

physical health and higher rates of multimorbidity (5, 8, 9). Not much is known about the impact of these developments on frailty prevalence and frailty-related mortality.

Monitoring trends in frailty and its association with mortality is important for health policy-makers, to enable projections about future health-care utilization. So far, this topic has received little attention in research. The few studies that have investigated birth cohort differences in frailty have found mixed results. One study that compared 2 cohorts of 70-year-olds in Sweden observed stable frailty levels (10), while studies in the United Kingdom and Hong Kong indicated that frailty is increasing in more recent cohorts of older adults (11–13). All these studies measured frailty with the frailty index (14), a commonly used frailty measure based on the deficit-accumulation approach. It counts age-related signs, symptoms, diseases, and disabilities and is regarded a sensitive frailty instrument (15, 16).

Two of the above-cited studies have also investigated cohort differences in the frailty-mortality relationship and found that the association between frailty and mortality remained the same or became slightly weaker (10, 11). However, both studies were based on only 2 time points, 20 to 30 years apart, which makes it difficult to identify trends. For that purpose, a minimum of 3 observations is needed.

The Longitudinal Aging Study Amsterdam (LASA) is one of the few cohort studies in older populations that has data available on frailty—measured by the frailty index—and mortality in the same age group at multiple time points, because of its cohort-sequential design (17, 18). The aim of the present study was to investigate trends in frailty and its relationship with mortality among older adults aged 64–84 years, using data from 6 time points in LASA, across a period of 21 years.

METHODS

Study population

We used data from LASA, which is a nationally representative study on physical, emotional, cognitive, and social functioning of older adults in the Netherlands. The sampling and measurements of LASA have been described elsewhere in greater detail (17, 19). In short, the study started in 1992 with a survey among older adults aged 55–84 years, based on a representative sample of the Dutch older population ($n = 3,107$). The data collection consists, among other methods, of face-to-face interviews and clinical tests in the home of the participants. Follow-up measurements are collected approximately every 3 years. A refresher cohort aged 55–64 years from the same sampling frame was added to the original sample in 2002–2003. This new cohort has the same follow-up schedule as the original cohort, with follow-up measurements every 3 years. As of the second LASA measurement wave (1995–1996), it is possible to measure frailty in LASA participants, due to some changes in measurement instruments. LASA is conducted in line with the Declaration of Helsinki and was approved by the medical ethics committee of the VU University Medical Centers. Informed consent was obtained from all study participants.

For the present study, we selected participants aged 64–84 years at each measurement wave between 1995 and 2012 (wave 1: 1995–1996, wave 2: 1998–1999, wave 3: 2001–2002, wave 4: 2005–2006, wave 5: 2008–2009, and wave 6: 2011–2012), to make the samples comparable in age over time. This resulted in partly independent samples, because at each measurement wave "new" participants (i.e., people who turned 64 years old) were included. Up to 2002, the newly included participants were from the original LASA cohort, and from 2005 they were from the LASA refresher cohort that was added in 2002–2003. On average, participants were included in 2.6 out of 6 measurement waves. The overlap between wave 1 and wave 6 was 14.1%. Participants were included in the analyses if they had valid data on mortality, frailty, and demographic characteristics. The pooled data set included 7,742 observations across 6 measurement waves from 2,874 participants. The number of participants at each wave varied from 1,141 to 1,549. Between measurement waves, 346 eligible participants (aged 64–84 years) dropped out because of reasons other than mortality (e.g., refusal, inability to contact). The proportion of nonmortality attrition was similar across measurement waves. The association between frailty and 4-year mortality was studied at each measurement wave, and the present study has a 21-year time span (1995–2016). An overview of the cohort-sequential design and mortality is provided in Figure 1.

Measures

Vital status and date of death were obtained from municipality registers up to January 2017. Its ascertainment was 99.4% complete. Mortality in LASA is very similar to that of the Dutch general older population (17). For all participants, at each measurement wave, we determined 4-year mortality (yes/no) since the date of the interview. We chose 4-year mortality to make maximum use of the data and to have a sufficient number of events to analyze. Moreover, from a clinical point of view, the short/medium follow-up time is the most relevant, given that it still offers possibilities to intervene and mitigate risks.

Frailty was measured by a 32-item frailty index. This frailty measure is based on the deficit-accumulation approach and has been validated in LASA (20). The frailty index was constructed following a standard procedure (21). The idea of the frailty index is that its content is not fixed. As long as certain requirements are met, such as a minimum of 30 age-related health deficits covering multiple domains or organ systems, the exact combination of health deficits does not matter. Various studies have shown that key characteristics of the frailty index are consistent across data sets with different frailty index operationalization (22). The frailty index in LASA consists of 32 health deficits from the physical, mental, and cognitive domain: self-reported chronic conditions (11 items), functional limitations (6 items), self-rated health (2 items), mental health (6 items from the Center for Epidemiologic Studies Depression scale), physical activity (1 item), memory complaints (1 item), cognition measured by subdomains from the Mini-Mental State Examination (4 items), and physical performance measured by gait speed (1 item). All deficits were scored between 0 and 1, with 0 indicating the absence of the deficit, and 1 the presence of the deficit. Details on all items and cutpoints of the LASA frailty index have been published previously (20). For the calculation of the frailty index, we allowed a maximum of 20% missing variables (≤ 6 items). This is a commonly used criterion, allowing for maximum use of available data (23). However, for most observations in the present study there were no missing variables (91.7% of the observations) or only 1–2 missing variables (7.7%) out of the total of 32 items of the frailty index. Frailty scores were calculated as follows: The sum of the health deficit scores was divided by the total number of items that were measured in a person (thereby taking into account the number of missing items, if any). For example, if a participant presents with 9 health deficits out of 32 items, the frailty index score is $9/32 = 0.28$. We applied the commonly used ≥ 0.25 cutoff to indicate the presence of frailty (24), as well as cutoffs to distinguish prefrailty (0.08–0.24) (24).
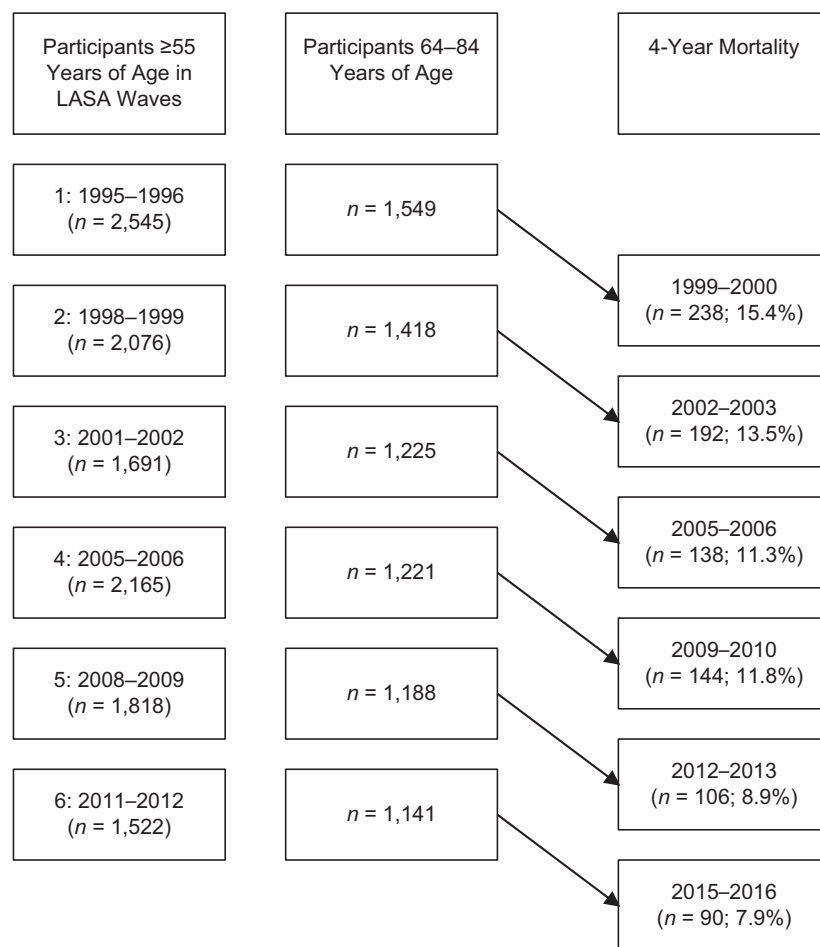
Participants ≥55 Years of Age in LASA Waves	Participants 64–84 Years of Age	4-Year Mortality
1: 1995–1996 (n = 2,545)	n = 1,549	1999–2000 (n = 238; 15.4%)
2: 1998–1999 (n = 2,076)	n = 1,418	2002–2003 (n = 192; 13.5%)
3: 2001–2002 (n = 1,691)	n = 1,225	2005–2006 (n = 138; 11.3%)
4: 2005–2006 (n = 2,165)	n = 1,221	2009–2010 (n = 144; 11.8%)
5: 2008–2009 (n = 1,818)	n = 1,188	2012–2013 (n = 106; 8.9%)
6: 2011–2012 (n = 1,522)	n = 1,141	2015–2016 (n = 90; 7.9%)

Figure 1. Design of the trend study and 4-year mortality rates among older adults aged 64–84 years participating in the Longitudinal Aging Study Amsterdam (LASA), the Netherlands, 1995–2016.

Statistical analysis

Descriptive analyses were conducted to characterize the study sample at each measurement wave. Trends in frailty were investigated using generalized estimating equation (GEE) analysis. All trend analyses were done for the total population and stratified by sex, because of the commonly observed sex differences in frailty (25). Logistic GEE analysis was done using a stationary M-dependent (Toeplitz) correlation structure, which accounts for within-subject correlations. Because we had 6 observations, this was a 5-dependent correlation structure. Although GEE and random effect models are both appropriate methods to study trends over time, it is more straightforward to estimate population average effects using GEE in case of binary outcomes (26). To show trends in frailty, we fitted a model that included time, age, and sex (where appropriate). The continuous time variable represents the increase in study years (0, 3, 6, 10, 13, and 16 years).

To investigate trends in the frailty-mortality relationship, again logistic GEE analyses with a 5-dependent correlation structure were performed, and 3 models were tested. In the first model, frailty was included, adjusted for age and sex (where appropriate). This model estimates an overall pooled association between frailty and 4-year mortality. Adjustment for age and sex was needed to make the distributions of the samples at each wave comparable over time, an important prerequisite for trend studies. In the second model, time was added, to show trends in 4-year mortality across the period of observation. Finally, a term for interaction between frailty and time was tested, in model 3. This interaction effect indicated whether there was a change over time in the frailty-mortality relationship. We did not consider other covariates, because the aim of our study was to show trends and not to explain them. We also tested a quadratic term for time, and an interaction effect between sex and frailty, but neither was statistically significant or included in the final model. To get a better insight into the frailty-mortality relationship across the full period of observation, we also performed logistic regression analyses at each measurement wave, with frailty as independent variable and 4-year mortality as outcome, adjusted for age and sex.

Table 1. Characteristics of the Study Sample at Each Measurement Wave for Participants Aged 64–84 Years in the Longitudinal Aging Study Amsterdam, the Netherlands, 1995–2012

Wave	No. of Participants	Age in Years, mean (SD)	Female Sex, %	Prefrailty[a],[b]		Frailty[a],[c]	
				%	95% CI	%	95% CI
1: 1995–1996	1,549	74.0 (6.1)	52.8	60.2	57.7, 62.6	20.9	19.1, 23.0
2: 1998–1999	1,418	73.6 (6.0)	55.2	60.0	57.5, 62.5	24.0	22.0, 26.2
3: 2001–2002	1,225	73.4 (5.7)	55.3	60.4	57.7, 63.0	25.4	23.2, 27.8
4: 2005–2006	1,221	72.8 (5.8)	54.9	59.0	56.3, 61.1	26.8	24.4, 29.3
5: 2008–2009	1,188	73.2 (6.0)	54.8	58.6	55.8, 61.3	25.7	23.4, 28.3
6: 2011–2012	1,141	73.0 (5.8)	54.6	57.2	54.3, 60.0	27.9	25.3, 30.6

Abbreviations: CI, confidence interval; SD, standard deviation.
[a] Prevalence derived from generalized estimating equation analyses, adjusted for age and sex.
[b] Prefrailty was defined as having a frailty index of 0.08–0.24.
[c] Frailty was defined as having a frailty index of ≥ 0.25.

We performed sensitivity analyses with a categorical time variable, additional adjustment for cohort and other covariates, prefrailty as separate category, and 3-year mortality as outcome (details in Web Material, available at https://doi.org/10.1093/aje/kwab018). We also repeated the main analyses with a continuous frailty index score, using linear or logistic GEE analyses. The level of statistical significance was set at $P < 0.05$ for main effects and $P < 0.10$ for interaction effects. P values were 2-sided. All analyses were conducted using SPSS, version 26 (IBM Corp, Armonk, New York).

RESULTS

The characteristics of the study sample at each measurement wave are shown in Table 1. In the later measurement waves (i.e., the more recent samples of 64- to 84-year-olds) a higher frailty prevalence was observed (Figure 2). From these analyses, it was estimated that frailty (frailty index $\geq$ 0.25) increased from 21% in 1995–1996 to 28% in 2011–2012. Chronic conditions (including incontinence) and self-rated health are the frailty index domains that have increased the most over time (results not shown).

Between 1995 and 2016, the unadjusted 4-year mortality rate among older adults aged 64–84 years decreased from 15.4% to 7.9% (Figure 1). This was confirmed by the association between time and mortality in the adjusted GEE analyses (Table 2, model 2). In the total sample (odds ratio (OR) = 0.97, 95% confidence interval (CI): 0.95, 0.98) and in both men (OR = 0.96, 95% CI: 0.94, 0.97) and women (OR = 0.98, 95% CI: 0.96, 1.00), a statistically significant decrease in 4-year mortality rates was observed. The downward trend in 4-year mortality was observed in both nonfrail and frail older adults. GEE analyses, adjusted for age and sex, showed that the estimated 4-year mortality decreased from 8.3% to 3.7% in nonfrail older adults, and from 26.4% to 19.1% in frail older adults (Figure 3).

Table 2 and Figure 4 show the associations between frailty and 4-year mortality over time. In the GEE analysis,

adjusted for age and sex (Table 2, model 1), there is a statistically significant overall pooled association between frailty and 4-year mortality (OR = 2.79, 95% CI: 2.39, 3.26). This pooled association was present in both men (OR = 2.98, 95% CI: 2.42, 3.68) and women (OR = 2.53, 95% CI: 2.02, 3.18). The association remained after adding covariates in models 2 and 3. Figure 4 illustrates how frailty is associated with mortality at each measurement wave.
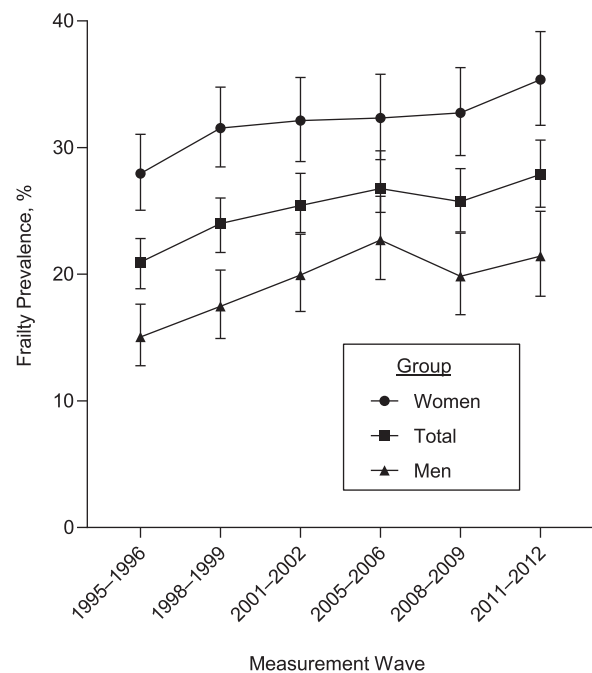

Figure 2. Trends in frailty according to sex among older adults aged 64–84 years participating in the Longitudinal Aging Study Amsterdam, the Netherlands, 1995–2012. Estimated frailty prevalence (frailty index $\geq$ 0.25) derived from generalized estimating equation analyses, adjusted for age and sex. Adjustment for sex was done only in the analysis of the total population.

Table 2. Generalized Estimating Equation Analyses of Associations Between Frailty and 4-Year Mortality Over Time for Participants Aged 64–84 Years in the Longitudinal Aging Study Amsterdam, the Netherlands, 1995–2016[a]

Variables	Total			Men			Women		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Model 1									
Frailty	2.79	2.39, 3.26	<0.001	2.98	2.42, 3.68	<0.001	2.53	2.02, 3.18	<0.001
Model 2									
Frailty	2.88	2.47, 3.37	<0.001	3.13	2.54, 3.87	<0.001	2.57	2.05, 3.24	<0.001
Time, years	0.97	0.95, 0.98	<0.001	0.96	0.94, 0.97	<0.001	0.98	0.96, 1.00	<0.05
Model 3									
Frailty	2.56	2.02, 3.23	<0.001	2.88	2.08, 4.01	<0.001	2.34	1.64, 3.33	<0.001
Time, years	0.96	0.94, 0.97	<0.001	0.95	0.93, 0.97	<0.001	0.97	0.94, 1.00	<0.05
Frailty × Time	1.02	0.99, 1.05	0.16	1.01	0.98, 1.05	0.51	1.01	0.98, 1.05	0.47

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] The analyses include 7,742 observations of 2,874 respondents. All models were adjusted for age and sex; sex adjustment only in the analysis of the total population. Frailty was defined as having a frailty index of ≥0.25.

Across all measurement waves, frailty (in a model together with age and sex) explained between 15% and 20% of the variance (Nagelkerke R^2) in 4-year mortality. There was no statistically significant interaction effect between frailty and
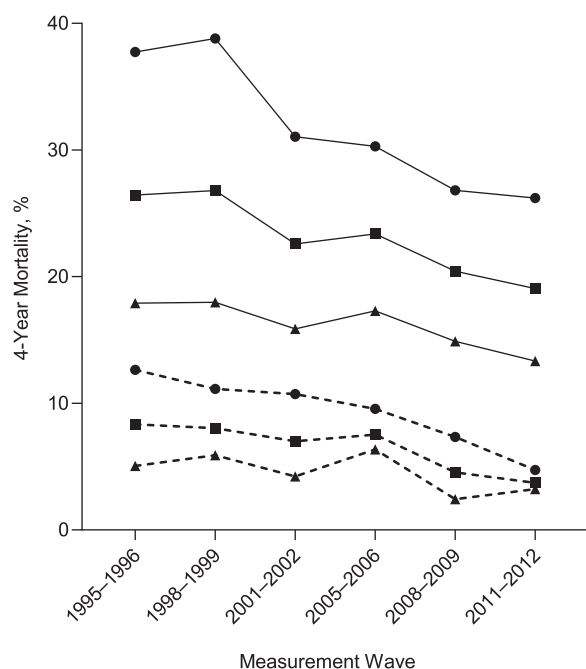

Figure 3. Trends in 4-year mortality according to frailty (frailty index ≥ 0.25) and sex among older adults aged 64–84 years participating in the Longitudinal Aging Study Amsterdam, the Netherlands, 1995–2016. Solid lines represent people with frailty (circle: men, square: total group, triangle: women), dashed lines represent people without frailty (circle: men, square: total group, triangle: women). Estimated proportion 4-year mortality derived from generalized estimating equation analyses, adjusted for age and sex. Adjustment for sex was done only in the analysis of the total population.

time (OR = 1.02, 95% CI: 0.99, 1.05; *P* = 0.16). Although the interaction effect points in the direction of a slightly stronger frailty-mortality relationship in later measurement waves, it was small and not statistically significant, meaning that mortality risk in older adults aged 64–84 years with frailty, compared with their nonfrail counterparts, remained the same over time.

We conducted several sensitivity analyses. First, using a categorical time variable in the GEE analyses instead of continuous time did not affect our main findings. The association between frailty and 4-year mortality became a bit stronger at later measurement waves, but this difference was not statistically significant (Web Table 1). Second, additionally adjusting the analyses for cohort effects, educational level, partner status, and smoking slightly changed the estimates, but the observed trends in frailty and the frailty-mortality relationship remained the same (Web Tables 2 and 3). Third, adding prefrailty as a separate category in the analyses on 4-year mortality showed a small association between prefrailty and 4-year mortality (OR = 1.34, 95% CI: 1.02, 1.76; *P* = 0.03), and this association became slightly stronger over time (OR = 1.06, 95% CI: 1.00, 1.12; *P* = 0.05) (Web Table 4). Fourth, the main results did not change when using 3-year mortality as outcome instead of 4-year mortality (Web Table 5). Finally, sensitivity analyses (GEE, adjusted for age and sex) with a continuous frailty index score (not shown in table) confirmed our results. During the period 1995–2012, frailty scores increased among older adults aged 64–84 years (1995–1996 estimated mean = 0.186; 2011–2012 estimated mean = 0.209; *P* < 0.001 for time). There was also an overall pooled association between the continuous frailty index score and 4-year mortality (per 0.01 increase on the frailty index, OR = 1.05, 95% CI: 1.04, 1.06; *P* < 0.001). The term for interaction between frailty index score and time indicated that the frailty-mortality relationship became slightly stronger over time, but the odds ratio was very small (OR = 1.00, 95% CI: 1.00, 1.02; *P* = 0.03).
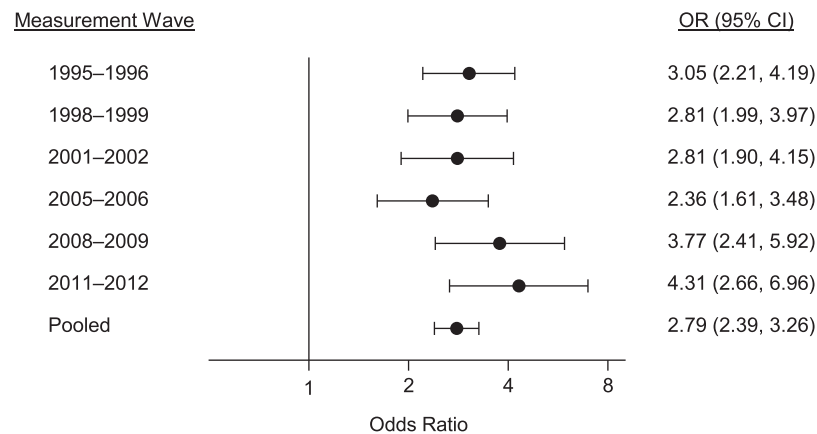
Measurement Wave   OR (95% CI)

Measurement Wave	OR (95% CI)
1995–1996	3.05 (2.21, 4.19)
1998–1999	2.81 (1.99, 3.97)
2001–2002	2.81 (1.90, 4.15)
2005–2006	2.36 (1.61, 3.48)
2008–2009	3.77 (2.41, 5.92)
2011–2012	4.31 (2.66, 6.96)
Pooled	2.79 (2.39, 3.26)

Odds Ratio

Figure 4. Association between frailty (frailty index ≥ 0.25) and 4-year mortality across waves and in a pooled analysis, for older adults aged 64–84 years participating in the Longitudinal Aging Study Amsterdam, the Netherlands, 1995–2016. Generalized estimating equation analysis was used for the pooled analysis and logistic regression for the wave-specific analysis; all adjusted for age and sex. CI, confidence interval; OR, odds ratio.

Across measurement waves, the model with age, sex, and a continuous frailty index score explained between 17% and 21% of the variance (Nagelkerke R^2) in 4-year mortality.

DISCUSSION

In this population-based study among older adults aged 64–84 years in the Netherlands, we investigated trends in frailty and its relationship with mortality across a period of 21 years (1995–2016). Three important conclusions can be drawn from our results: Frailty prevalence rates have increased in more recent generations of older adults; 4-year mortality rates declined in both frail and nonfrail older people; and there was a stable association between frailty and mortality.

Our results revealed that the proportion of frail older adults in the community is gradually increasing in more recent cohorts. This could be the result of increased life expectancy and the fact that people tend to live longer with chronic conditions than before (5). Our findings extend previous research from Hong Kong and the United Kingdom, which also found higher frailty levels in more recent generations of older adults (11–13). One study from Sweden observed stable frailty levels, but this work was based on a comparison of 2 cohorts of 70-year-olds from many years ago (measured in 1971 and 2000) (10).

Our study confirms the well-known association between frailty and mortality (4). Both men and women with frailty were at increased risk of 4-year mortality across the full study period. Although we observed slightly stronger frailty-mortality relationships in later measurement waves, this increase was not statistically significant. This means that, while in recent decades favorable trends have been observed in the excess mortality of various chronic conditions, such as heart disease (6), the excess mortality rates of frailty have remained the same in different historical periods. A previous study in the United Kingdom found the same when comparing 2 cohorts of older adults aged 65 years or older

in 1991 and 2011. In contrast, work from Sweden showed that the frailty-mortality association became weaker over time (10). However, this study compared 2 cohorts 30 years apart, in a very specific age-group (70-year-olds) and—as mentioned before—in a different historical period.

The results of our study have implications for clinical practice and public health. We observed an increase in the prevalence of frailty, which could in turn have an impact on health-care utilization. Combined with the aging of the population, this impact could be even stronger as the number of older adults in society grows (5), of whom a larger proportion will be frail. Therefore, it is likely that the frailty-related burden for the health-care system will increase. Despite many interventional programs focused on reducing frailty and its adverse outcomes (27–29), these initiatives do not seem to have resulted in decreased excess mortality rates of frailty in the past 2 decades. Therefore, more research is needed to identify interventions that can effectively prevent frailty progression and improve health outcomes in frail older adults. At the same time, it remains to be seen whether the excess mortality rates of frailty can be reduced in the same way as we have seen for various chronic conditions in the past few decades. Perhaps, it is much more difficult to reverse frailty—an indicator of biological aging—than the impact of a single disease (27).

Our study has several strengths. We used nationally representative data from a large study among older adults in the Netherlands. The cohort-sequential design, with exactly the same measurement instruments at each measurement wave, allowed for identification of secular trends in frailty. Moreover, this was the first study to investigate trends in frailty and its association with mortality over an extended time period that made use of data from multiple time points only 3 years apart. Therefore, our study is better able to capture trends in specific periods, compared with previous studies that made use of only 2 time points 20 to 30 years apart (10, 11) or data from age cohorts that were all measured at the same moment (12).

Nevertheless, this study also has some limitations. First, this study was only descriptive. Explaining trends is an important next step to understand secular trends in frailty and its relationship with mortality. However, it is also rather complex to explain 3 different trends (in predictor, outcome, and association) within the same study. We therefore considered this to be beyond the scope of the present study. Second, our analyses were done on samples that were partly overlapping. A design with multiple independent samples at various time points, with longitudinal data on mortality, would be ideal. However, such data on frailty is not available. LASA is one of the few studies worldwide that allows for examination of trends in frailty over a period of more than 20 years, with a cohort-sequential design with partly independent samples (17). Third, we interpret our findings as trends, but they might also come partially from changes in reporting behavior in more recent cohorts. It is well-known that higher expectations of health care and lower tolerance of health problems can lead to changes in self-report in more recent generations of older adults (30, 31). At the same time, this does not apply to all items of the frailty index, many of which are based on standardized instruments or performance measures. Fourth, we have not examined the population attributable fraction of mortality explained by frailty. Even though the association between frailty and 4-year mortality did not change over time, the rise in the prevalence of frailty combined with decreased overall mortality might have led to changes in the population attributable fraction of frailty for mortality. This should be addressed in future research. Finally, in our study we used only one out of many available frailty instruments (32, 33). Although our frailty index is one of the most commonly used and widely validated frailty instruments, it would be interesting to see whether the results would be the same with other important frailty measures, such as the physical frailty phenotype (34).

To conclude, this trend study among older adults aged 64–84 years in the Netherlands indicated that higher frailty prevalence rates were observed in more recent generations of older adults, together with a stable trend in the frailty-mortality relationship. This means that the proportion of frail older adults in the community is increasing, while the excess mortality rates of frailty remained the same. This is important information for health policy-makers and clinical practice, showing that continued efforts are needed to reduce frailty and its negative health consequences.

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