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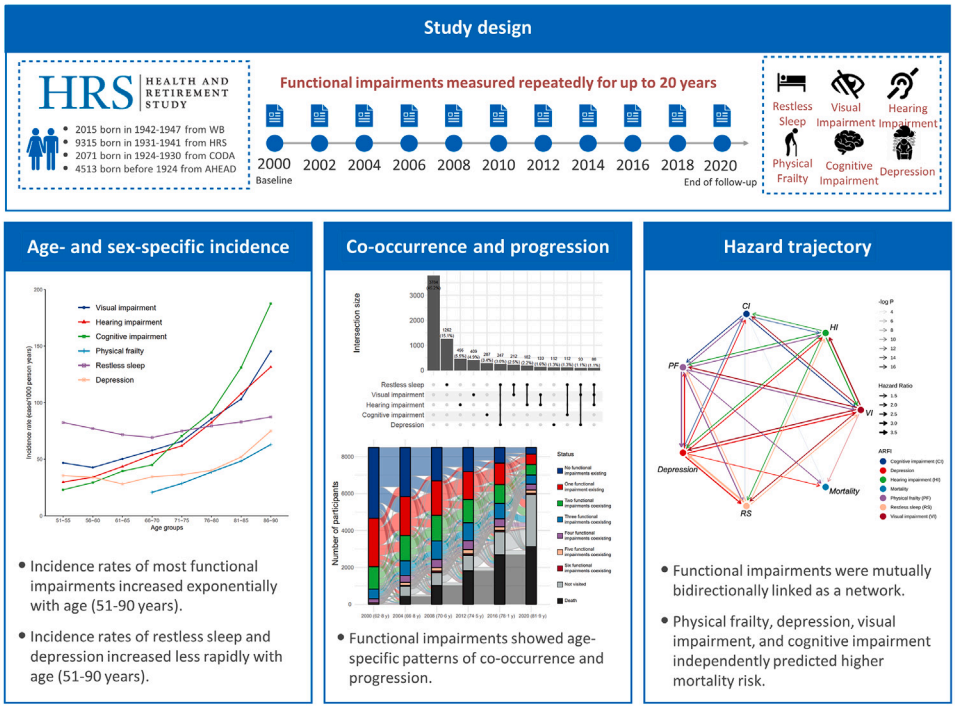

Chen et al., Progression and trajectory network of age-related functional impairments and their combined associations with mortality

Hui Chen, Binghan Wang, Rongxia Lv, ..., Xiaolin Xu, Yuan Ma, Changzheng Yuan

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Highlights

Incidence rates of certain functional impairments increase exponentially with age

Distinct patterns of functional impairments were observed across age groups

Six functional impairments are bidirectionally related to each other during follow-up

Number of functional impairments predicts mortality risk in a dose-response manner

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Progression and trajectory network of age-related functional impairments and their combined associations with mortality

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SUMMARY

Age-related functional impairments (ARFIs) contribute to the loss of independence in older adults, but their progressions, interrelations, and combined relations with mortality are largely unknown. We conducted a prospective study among 17,914 participants in the Health and Retirement Study (2000–2020). The incidence rates of visual impairment, hearing impairment, physical frailty, and cognitive impairment increased exponentially with age, while those of restless sleep and depression increased relatively slowly. These ARFIs were associated with each other in temporal sequence and constituted a hazard network. We observed a dose-response relationship between the number of ARFIs and mortality risk, and the dyads involving physical frailty demonstrated the strongest associations with mortality. Our findings may assist in the identification of individuals at higher mortality risk and highlight the potential for future investigations to explore the impact of multiple ARFIs in aging.

INTRODUCTION

In the context of worldwide population aging,[1] healthy longevity has become increasingly critical.[2,3] Aging is characterized by changes in multiple functions, including sensory, physical, mental, and cognitive function,[4,5] which largely influence the independence, life quality, and longevity of older adults. The processes underlying these functional changes are highly entwined,[6] and age-related functional impairments (ARFIs) often co-exist and co-occur.[7,8] For example, physical frailty was associated with a higher risk of subsequent cognitive impairment, disability, and death[5,9,10]; cognitive decline was prospectively related to increased risks of falling and frail symptoms[11]; and a panel of functional markers of aging (vision, hearing, vibration sense, forced expiratory volume, and grip strength) might predict cognitive performance.[12] Therefore, these relations may constitute a network and there warrant investigations into their complex interrelations.

In the field of age-related diseases,[13,14] graph-based trajectory networks have provided a comprehensive landscape of the bidirectional associations between multiple diseases and thus distinguished itself with traditional approaches to establishing disease-disease associations. For instance, a prospective study in the Danish National Patient Register presented a trajectory network to display the multimorbidity spectrum of a specific disease using a single connected graph.[15] Another cohort study examined the state transitions among age-related diseases using multistate models.[16] However, these studies all focused on the clinical diagnosis of diseases, while there are few attempts to uncover the trajectory networks of ARFIs, which requires frequent and comprehensive assessments of the functions of interest and may be more relevant to the ability of daily living of older adults. In addition, although previous studies have identified the associations of individual ARFIs with mortality,[10,17–19] their combined relations to mortality remained largely unknown.

Therefore, we hypothesize that ARFIs are associated with each other and contribute to the risk of mortality in a dose-response manner. In the Health and Retirement Study (HRS), we characterized the trajectory networks of ARFIs and their associations with mortality in two decades of biennial follow-ups. Our findings will provide important insights into understanding the aging processes by disentangling the sequential associations between ARFIs and their associations with mortality.

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Table 1. Baseline characteristics of the study participants in the Health and Retirement Study

		Birth cohorts			
		WB	HRS original cohort	CODA	AHEAD
Characteristics	Overall (N = 17,914)	(N = 2,015)	(N = 9,315)	(N = 2,071)	(N = 4,513)
Age, years (mean [SD])	67.5 (9.6)	54.8 (2.8)	63.0 (4.9)	72.3 (2.2)	80.2 (5.2)
Female, N (%)	10,300 (57.5)	975 (48.4)	5,083 (54.6)	1,249 (60.3)	2,993 (66.3)
Race, N (%)					
White	14,852 (82.9)	1,618 (80.3)	7,564 (81.2)	1,797 (86.8)	3,873 (85.8)
Black	2,442 (13.6)	303 (15.0)	1,405 (15.1)	185 (8.9)	549 (12.2)
Others	615 (3.4)	93 (4.6)	343 (3.7)	89 (4.3)	90 (2.0)
Education, N (%)					
Lower than high school	4,872 (27.2)	290 (14.4)	2,339 (25.1)	592 (28.6)	1,651 (36.6)
GED	770 (4.3)	100 (5.0)	467 (5.0)	81 (3.9)	122 (2.7)
High school	5,666 (31.6)	584 (29.0)	3,003 (32.2)	646 (31.2)	1,433 (31.8)
Some college	3,433 (19.2)	487 (24.2)	1,808 (19.4)	384 (18.5)	754 (16.7)
College and above	3,173 (17.7)	554 (27.5)	1,698 (18.2)	368 (17.8)	553 (12.3)
BMI, kg/m^2 (mean [SD])	27.1 (5.3)	28.4 (5.8)	27.7 (5.4)	26.8 (4.9)	25.25 (4.7)
Household income, dollars (mean [SD])	14,741.9 (59,065.1)	21,637.9 (81,384.0)	17,374.1 (69,236.2)	9,459.6 (25,650.5)	8,654.2 (24,723.7)
Drinking status, N (%)					
Never	9,826 (54.9)	884 (43.9)	4,817 (51.7)	1,166 (56.3)	2,959 (65.6)
Former	3,257 (18.2)	442 (21.9)	1,735 (18.6)	385 (18.6)	695 (15.4)
Current	4,827 (27.0)	689 (34.2)	2,761 (29.6)	520 (25.1)	857 (19.0)
Smoking status, N (%)					
Never	7,211 (40.6)	791 (39.3)	3,437 (37.4)	860 (41.5)	2,123 (47.3)
Former	7,882 (44.4)	777 (38.6)	4,063 (44.2)	972 (46.9)	2,070 (46.2)
Current	2,667 (15.0)	447 (22.2)	1,690 (18.4)	239 (11.5)	291 (6.5)
Vigorous physical activity >3 times/ week, N (%)[a]	7,570 (42.3)	991 (49.2)	4,360 (46.8)	878 (42.4)	1,341 (29.7)
Visual impairment, N (%)	3,900 (21.9)	332 (16.5)	1,776 (19.1)	414 (20.1)	1,378 (30.9)
Hearing impairment, N (%)	3,629 (20.3)	243 (12.1)	1,585 (17.0)	437 (21.1)	1,364 (30.3)
Cognitive impairment, N (%)	4,589 (27.8)	285 (15.1)	1,692 (19.7)	668 (34.2)	1,944 (47.4)
Physical frailty, N (%)	2,026 (11.3)	115 (5.7)	840 (9.0)	243 (11.7)	828 (18.4)
Restless sleep, N (%)	5,362 (33.1)	634 (33.9)	2,788 (32.7)	621 (32.3)	1,319 (33.9)
Depression, N (%)	1,948 (12.0)	214 (11.5)	955 (11.2)	209 (10.9)	570 (14.6)

SD, standard deviation; GED, general educational development; BMI, body mass index; WB, the War Baby cohort born in 1942–1947; HRS, the Health and Retirement Study original cohort born in 1931–1941; CODA, the Children of the Depression cohort born in 1924–1930; AHEAD, the Asset and Health Dynamics Among the Oldest Old cohort born before 1924. Missing values were omitted from frequency counting and mean calculation.

[a]Vigorous physical activity includes running, jogging, swimming, cycling, aerobics or gym workout, tennis, and digging.

RESULTS

Participants characteristics

We included four birth cohort in the analyses, including the War Babies (WB, born in 1942–1947), the HRS original cohort (born in 1931–1941), the Children of the Depression (CODA, born in 1924–1930), and the Asset and Health Dynamics Among the Oldest Old (AHEAD, born before 1924). Among the 17,914 participants included from the four birth cohorts, 57.5% were female, 82.9% were White, and the mean (SD) of baseline age was 67.5 (9.6) years (Table 1). Participants in earlier birth cohorts were more likely to be female, less educated, never drinkers, never smokers, and less physically active. For example, compared to the WB participants (mean [SD] age 54.8 [2.8] years), the AHEAD participants (mean [SD] age 80.2 [5.2] years old) were more likely to be less educated (1,651 [36.6%] vs. 290 [14.4%] with the highest education level lower than high school), never drinkers (2,959 [65.6%] vs. 884 [43.9%]), never smokers (2,123 [47.3%] vs. 791 [39.3%]), and have less vigorous physical activity (1,341 [29.7%] vs. 991 [49.2%]). The age- and sex-adjusted incidence of the ARFIs did not differ by birth cohorts (p values for visual

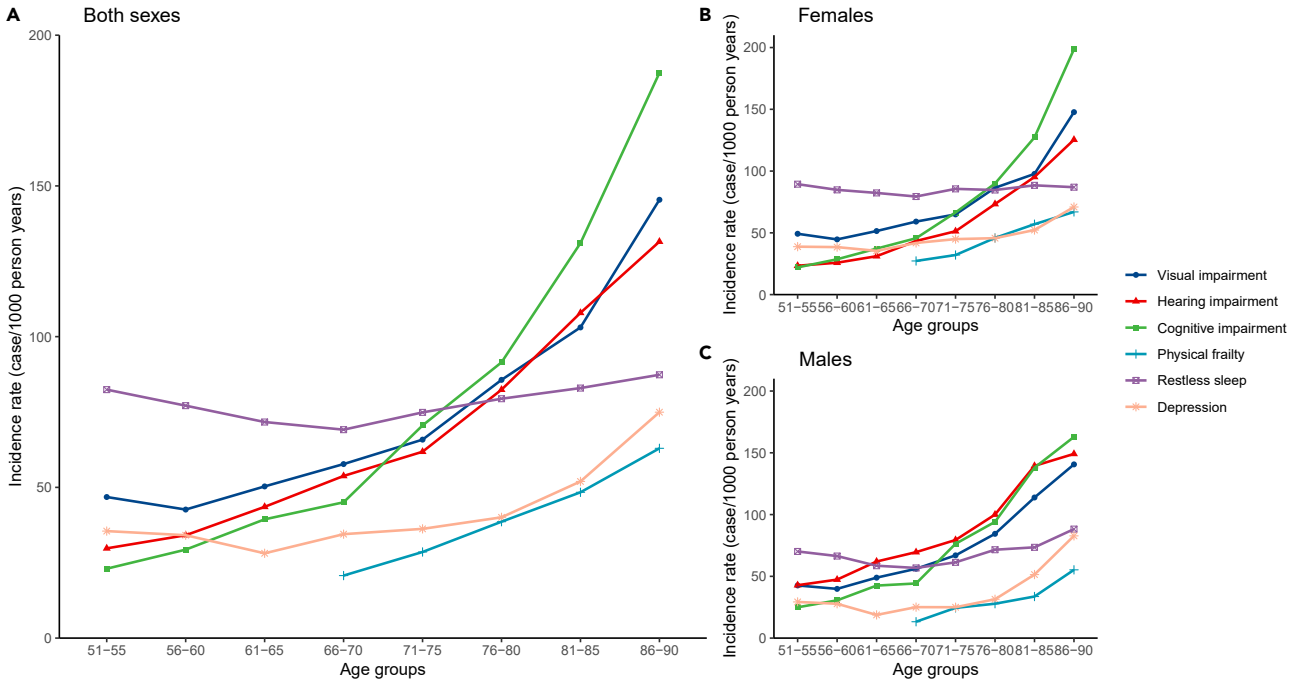

Figure 1. Age- and sex- specific incident rates of age-related functional impairments

(A) Age-specific incident rates of age-related functional impairments; (B) incident rates of age-related functional impairments among female participants; (C) incident rates of age-related functional impairments among male participants. Physical frailty indicators are only measured among participants aged over 65.

impairment [VI]: 0.578; hearing impairment [HI]: 0.553; cognitive impairment [CI]: 0.838; physical frailty [PF]: 0.561; restless sleep [RS]: 0.158; and depression: 0.070).

Overall, age-, and sex-specific four-year incidence rates of ARFIs

During follow-up (median [interquartile range], 12 [6–18] years), we identified 5,934 incident visual impairment cases, 5,306 incident hearing impairment cases, 4,951 incident restless sleep cases, 6,656 incident cognitive impairment cases, 5,431 incident physical frailty cases, and 3,679 incident depression cases. The incidence rates were 59.3, 52.1, 42.5, 31.7, 75.6, and 35.6 cases/1,000 person-years, respectively (Table S1).

The incidence rates of visual impairment, hearing impairment, cognitive impairment, and physical frailty were exponentially higher in older ages (*P* for linear and exponential trends both <0.001; Figure 1A), while those for depression and restless sleep increased relatively slowly. For example, the incidence rate for cognitive impairment was 45.0 cases/1,000 person-years for participants aged 66–70 years old and 91.5 cases/1,000 person-years for participants aged 76–80 years old. The incidence rate of restless sleep was the highest among all ARFIs before the age of 75 years but was surpassed by cognitive impairment in older age groups.

We observed similar trends for women and men (Figures 1B and 1C). Female participants had higher incidence rates of restless sleep (84.3 vs. 63.6 cases/1,000 person-years), physical frailty (38.5 vs. 22.8 cases/1,000 person-years), and depression (41.4 vs. 27.3 cases/1,000 person-years), while male participants had higher incidence rate of hearing impairment (67.4 vs. 43.1 cases/1,000 person-years, $p < 0.001$ for all aforementioned tests).

Co-existence and progression of ARFIs

As study baseline (2000), 4,529 (28.6%) participants had co-existing ARFIs (20.1% in WB, 24.0% in HRS, 30.2% in CODA, and 42.0% in AHEAD), and patterns of their co-existence varied by age (Table S2; Figure 2). During follow-up (2000–2020), the proportion of surviving respondents with co-existing ARFIs increased from 28.6% to 64.2% (Tables S3 and S4) in all birth cohorts (Figure 2). For example, the proportion of WB participants with co-existing ARFIs increased from 20.1% (367) to 55.1% (374), and that for the AHEAD cohort increased from 42.0% (1,582) to 90.5% (114).

Hazard trajectory network of functional impairments

All six ARFIs were significantly related to each other and constitute a hazard trajectory network (Figure 3; Table S5). For example, visual impairment predicted higher risks of hearing impairment (hazard ratios [HRs] 2.48, 95% confidence interval [CI] 2.29–2.69), depression (2.18, 2.00–2.39), physical frailty (2.08, 1.92–2.24), restless sleep (1.72, 1.59–1.86), and cognitive impairment (1.63, 1.53–1.74). Each additional ARFI was

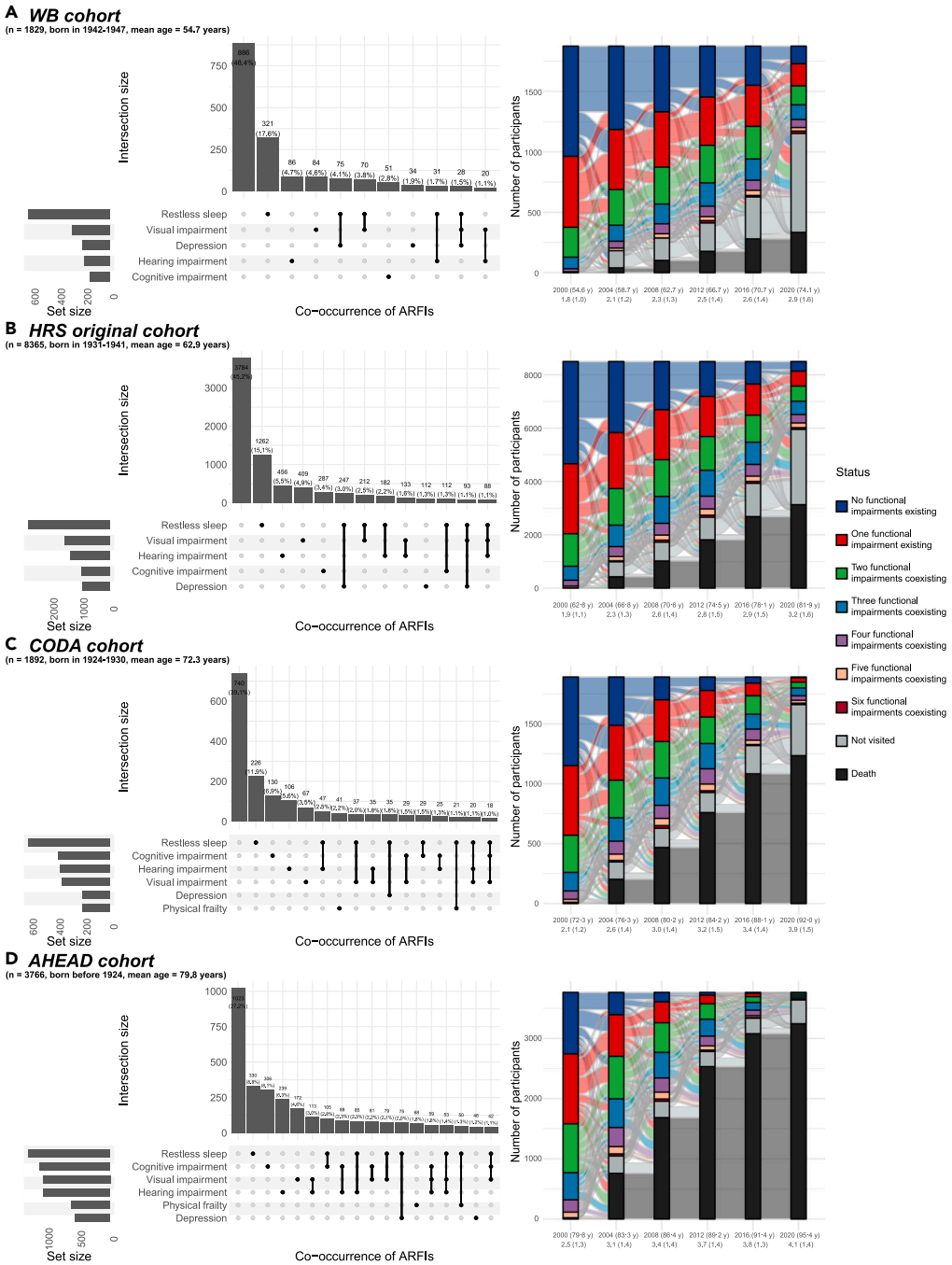

Figure 2. Co-existence and progression of age-related functional impairments by birth cohorts

(A) WB cohort: the War Baby cohort born in 1942–1947.

(B) HRS cohort: the Health and Retirement Study original cohort born in 1931–1941.

(C) CODA cohort: the Children of the Depression cohort born in 1924–1930.

(D) AHEAD cohort: Asset and Health Dynamics Among the Oldest Old cohort born before 1924. Combinations with ≤1% cases within each cohort were omitted in the left panel. The labels of the x-axis in Sankey diagrams (the right panel) were expressed as the year (mean age) and mean (standard deviation) number of ARFIs.

related to 13% higher hazard of mortality (HR: 1.13, 95% CI: 1.11–1.15). Compared to participants without any ARFI, participants with 1, 2, 3, 4, and 5 or 6 ARFIs were at 12% (6%–18%), 35% (26%–44%), 55% (43%–68%), 43% (27%–61%), and 75% (50%–104%) higher mortality risk, respectively (Figure 4A). The dyads most strongly associated with the risk of mortality were those involving physical frailty (Figure 4B), particularly

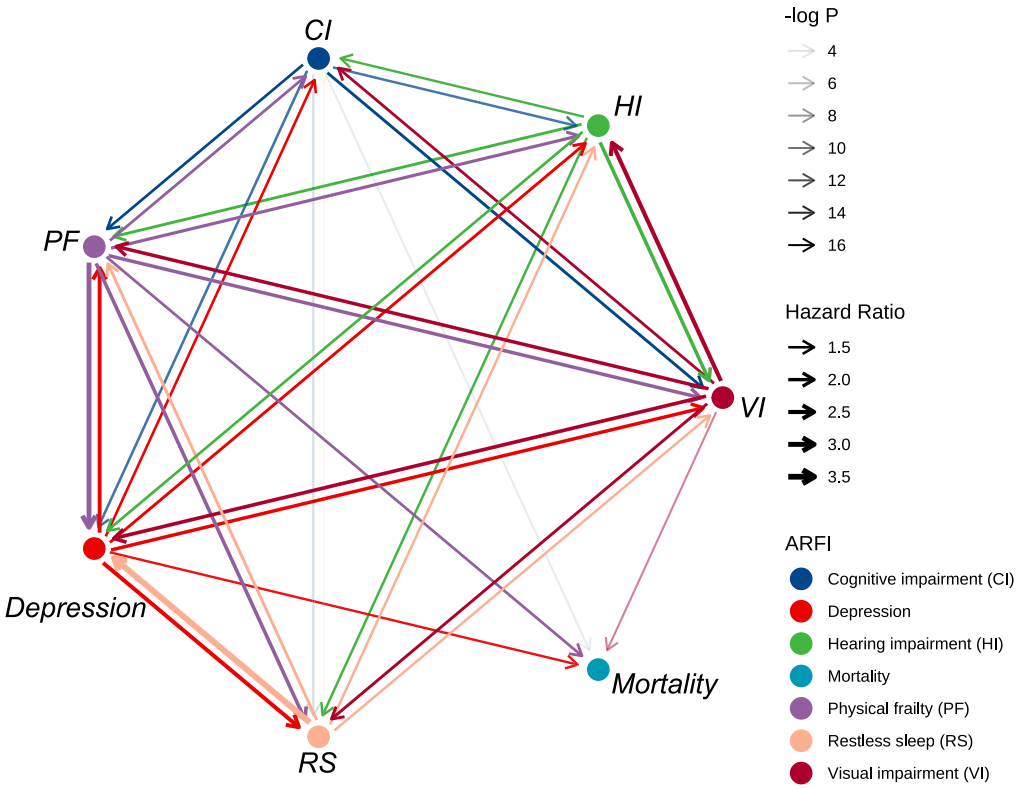

Figure 3. Hazard trajectory network of age-related functional impairments and mortality

ARFI: age-related functional impairment, VI: visual impairment, HI: hearing impairment, CI: cognitive impairment, PF: physical frailty, RS: restless sleep. The directed edges indicated the temporally sequential associations between ARFIs and mortality (nodes), the transparency represented the statistical significance (-log *P*), and the thickness indicated the magnitudes of relations (thicker arrow for larger HR). All analyses were adjusted for age, sex (male/female), BMI, race (White/Black/Others), education (lower than high school/general educational development/high school/some college/college and above), household income, smoking status (never/former/current), drinking status (never/former/current), and vigorous physical activity (whether more than three times a week) and other ARFIs.

physical frailty combined with cognitive impairment (HR: 1.78, 95% CI: 1.59–1.99), visual impairment (1.68, 1.53–1.85), and depression (1.58, 1.42–1.75). Furthermore, physical frailty, depression, visual impairment, and cognitive impairment each independently predicted 59% (49%–69%), 38% (30%–46%), 19% (13%–26%), and 13% (6%–21%) higher risk of all-cause mortality, respectively. These associations were similar between sexes (Table S6). The trajectory network remained similar when we excluded participants with baseline chronic conditions, restricted

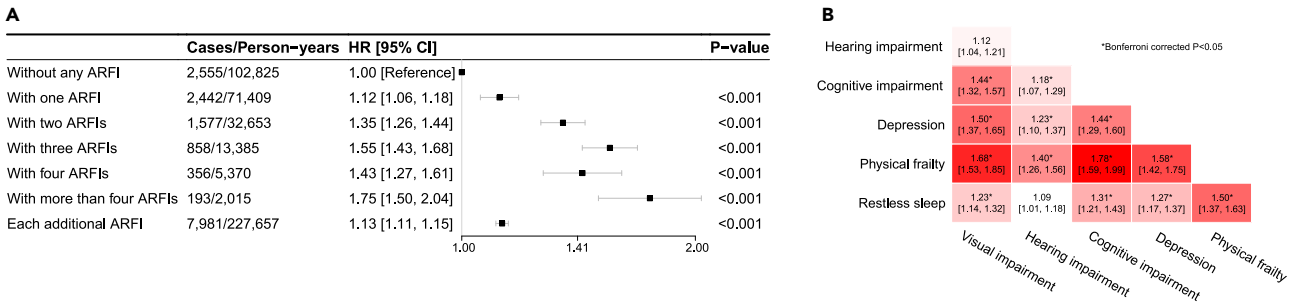

Figure 4. Hazard ratios and 95% confidence intervals of mortality according to age-related functional impairments

(A) Hazard ratios (squares) and 95% confidence intervals (error bars) of mortality according to the number of age-related functional impairments; (B) hazard ratios and 95% confidence intervals of mortality according to the dyads of age-related functional impairments. ARFI, age-related functional impairment; HR, hazard ratios; CI, confidence intervals. The HRs were adjusted for age, sex (male/female), BMI, race (White/Black/Others), education (lower than high school/general educational development /high school/some college/college and above), household income, smoking status (never/former/current), drinking status (never/former/current), and vigorous physical activity (whether more than three times a week) at baseline. The HRs of dyads of baseline ARFIs were additionally adjusted for the presence of other ARFIs.

our analyses to participants without any ARFIs at baseline, and treated mortality as a competing event when analyzing associations between ARFIs (Table S7).

DISCUSSION

In this two-decade prospective study, the incidence rates of visual impairment, hearing impairment, cognitive impairment, and physical frailty and their co-existing complexity increased with age. We constructed a hazard trajectory network showing that the ARFIs were bidirectionally associated in temporal order. A larger number of ARFIs was related to higher all-cause mortality risk in a dose-response manner, with independent associations observed for visual impairment, physical frailty, cognitive impairment, and depression. ARFI dyads involving physical frailty showed the strongest associations with mortality risk.

Our findings on the age- and sex-specific incidence rates of AFRIs echoed and extended current literature in this field.[20–25] For instance, the incidence rate of cognitive impairment was 74.8 cases/1,000 person-years in an 8-year cohort study among American adults aged 72–80,[26] which is similar to our results (79.6 cases/1,000 person-years). The observed sex and age disparities in incidence rates also corresponded to prior knowledge.[22,24,27–29] For example, a review reported that women had a greater incidence of depression than men, and the incidence rate decreased after the age of 50 years Also, our results echoed the established knowledge that the risk of impairments in sensory, physical, and cognitive function was higher in older ages.[23,25,30–32] Compared to other ARFIs, the exponential increase periods for restless sleep and depression traits may have occurred earlier and may have higher incidence in the middle-aged population.[24] Therefore, our observation that their incidence rate increased less rapidly in older adults should be interpreted with caution.

Based on these findings, we further looked into their patterns of co-existence and progression, which were rarely reported in previous studies. Current literature on multimorbidity has focused on the co-existence of age-related diseases.[14,15,33–35] For example, a matched case-control study in a claim database reported that older age was related to greater risk of and more complex patterns of comorbidity of five pulmonary diseases and metabolic disease.[35] We extended this framework to the ARFIs, which was directly related to the independence and well-being of older adults. Our findings implied that the aging process was a systematic deterioration of multiple functions, and healthy longevity requires holistic consideration of the intactness of multiple systems. Meanwhile, we discovered more complicated patterns of co-existence of ARFIs as age increased, which underscored the need for individualized early prevention, intervention, and care.

Furthermore, we constructed a hazard trajectory network of these ARFIs following an analysis framework of aging-related diseases.[13–15,33] In 7.2 million Danish patients, Siggaard et al. constructed a disease trajectory browser to illustrate the connection network of diagnosed diseases.[15] Using claim data, Jin and colleagues also conducted a network analysis for diseases with strong associations.[33] We assessed the associations between ARFIs, based on previous studies that have discovered unidirectional[36–38] or bidirectional relations between sensory impairments, such as vision and hearing, depression, and cognitive impairment.[36–40] For example, a meta-analysis of longitudinal studies indicated that visual impairment was associated with a 66% higher risk of cognitive impairment, and that cognitive impairment was also associated with the incidence of visual impairment.[40] As for the risk of mortality, our findings also align with several long-term follow-up cohort studies.[17,18,41,42] Additionally, we observed a dose-response relationship between the number of ARFIs and mortality risk, with a greater risk among participants with a higher number of ARFIs. Our findings suggested that dyads involving physical frailty were particularly associated with an increased risk of mortality. These associations did not differ by sex, which partly echoed previous report from the Danish National Patient Register that most disease associations did not differ by sex (25,508 out of 27,185 were not sex-specific), although disease progression patterns may differ between females and males.[29] Specifically, in the Danish population, the incidence rates of many diseases differed between sexes. While most observed associations between diseases are non-sex-specific, they did reveal sex differences for many important and relevant associations. For example, the association of paroxysmal tachycardia with chronic ischemic heart disease was reversed between women (relative risk: 1.17, 95% Bayesian credible interval: 1.12–1.22) and men (0.94, 0.90–0.97). As for the associations between ARFIs, the findings from the Danish cohort were similar and mostly non-sex-specific (Table S8). For example, the pairwise associations of depression with sleep disorders were similar in men and women. Nevertheless, there still warrants large-scale studies to test whether there is any sex difference in the associations because of the limitations of sample sizes. To our knowledge, the current study was one of the few that assessed the associations between a panel of ARFIs and mortality. By constructing a hazard trajectory network, the findings added to existing literature in the field of functional aging and provided clues for preventing and controlling multiple ARFIs to achieve healthy longevity.

Our findings have both clinical relevance and public health implications. As ARFIs result from multi-system pathophysiological changes,[6] active and healthy aging should focus on the prevention of multiple function impairments as a whole[43] to prolong life expectancy and reduce disability.[44] In clinical practice, the diagnosis of a single ARFI may predict higher risk of other ARFIs, which could help identify individuals at higher risks of other ARFIs and mortality. Considering individuals with distinct patterns of functional limitations may require various health and social services,[45] our findings may open a gate to inform future strategies of personalized medicine for the aging population. Furthermore, the combined associations of the ARFIs (their dyads and the number of ARFIs) with mortality might be useful to identify potentially high-risk individuals in clinical and public health practice.[46] Future research could combine functional changes, physiological mechanisms, and disease occurrence for early and precise identification of high-risk populations.

Although the underlying mechanism remains unclear and complex, several possible pathways could connect changes from biological aging at molecular and organ levels to phenotypic aging at the system level for individuals, and eventually functional aging that contribute to disability and dependence.[47] For example, studies have demonstrated that telomere shortening could indicate the cellular senescence,[48–50] which may trigger biological changes in organs and thereafter cause phenotypic aging for individuals and cause functional limitations, such as cognitive decline[51] and frailty.[50] Several studies have also provided evidence that telomeres were associated with changes in sensory and

mental function.[51,52] Another possible common cause is brain aging,[53] which reduces the general fitness of the body and leads to age-related functional changes.[12] For instance, atrophy of brain regions such as the striatum, amygdala, and hippocampus in aging may increase the vulnerability to depression,[54] which also affects the pathways of sensory function.[55] Thus, the complex intertwining of ARFIs could be explained by certain specific mechanisms or pathways at different levels of aging.

Limitations of the study

Despite of the strengths in the prospective design, long-term follow-up, and the frequent measurement of functional phenotypes, several limitations should be taken into account when interpreting our findings. First, the ascertainment of ARFIs was based on self-reports or questionnaires[56] and is subject to misclassification. While previous studies have shown the acceptable reproducibility and validity of these definitions,[57–60] future studies using gold-standard clinical measurements are warranted.[61] Second, we focused on six common ARFIs and did not include others (such as taste impairment) due to data limitations. In addition, we did not account for incident diseases such as cancer and stroke, which could be incorporated in future studies to better understand the aging process. As our findings are based on a US cohort, their generalizability to other populations should be confirmed. Finally, while our hazard network accounts for the temporal sequence of ARFIs, it does not necessarily indicate causal relations, as residual confounding and reverse causation could still exist given the observational nature of our study.

Overall, in this prospective study, the incidence rates of several ARFIs (i.e., visual impairment, hearing impairment, physical frailty, and cognitive impairment) increased exponentially with age, whereas others (restless sleep and depression) increased less rapidly. Using a hazard trajectory network, we found that the ARFIs were sequentially related to each other, and the number of them was associated with higher mortality risk in a dose-response manner. To achieve healthy longevity, integrated strategies for preventing and managing multiple ARFIs are urgently needed.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.108368.

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AUTHOR CONTRIBUTIONS

C.Y. and H.C. designed the study; B.W., H.C., and T.Z. performed the statistical analyses; B.W. and T.Z. interpreted the data; H.C. and B.W. drafted the manuscript; R.L., J.S., and X.X. further revised the manuscript; C.Y. supervised the data analysis and interpretation; C.Y. had the primary responsibility for the study final content. All authors critically reviewed the manuscript and approved the final draft.

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
The Health and Retirement Study	The Health and Retirement Study	https://hrs.isr.umich.edu/
Sex-specific relative risks of disease-disease associations in the Danish population	Siggaard et al.[15]	https://doi.org/10.1038/s41467-019-08475-9
Software and algorithms		
R	R Project for Statistical Computing	https://www.r-project.org
ComplexUpset (R package)	Michał Krassowski[62]	https://krassowski.github.io/complex-upset/index.html
ggalluvial (R package)	Brunson et al.[63]	http://corybrunson.github.io/ggalluvial/
igraph (R package)	The igraph core team	https://igraph.org/
Other		
R code for analysis	This paper	https://github.com/YuanLabZJU/arfis-network-hrs

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Changzheng Yuan (chy478@zju.edu.cn).

Materials availability

The study did not generate any new materials.

Data and code availability

- Data described in the manuscript and the codebooks are publicly available (https://hrs.isr.umich.edu/).
- Analysis code can be found in the Github (https://github.com/YuanLabZJU/arfis-network-hrs).
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

The HRS is a national longitudinal study among middle-aged or older adults in the United States. Participants born in 1931–1941 were recruited in 1992 (HRS original cohort). In 1993/1994, participants born before 1924 were included as the Asset and Health Dynamics Among the Oldest Old (AHEAD) cohort. In 1998, participants born in 1924–1930 (Children of the Depression, CODA) and 1942–1947 (War Babies, WB) were enrolled. The four non-overlapping cohorts formed a nationally representative sample of US adults aged 50 years or older. We stratified our analysis by birth cohorts where applicable. The recruitment and data collection processes of the four sub-cohorts were similar, enabling the cross-cohort comparisons for the associations between cohorts.[64] Participants were revisited biennially through telephone, Internet, or face-to-face interviews, with an overall response rate of ~85%.[64] More detailed information can be found elsewhere (https://hrs.isr.umich.edu/). This HRS was approved by the Institute for Social Research of the University of Michigan (IRB Protocol: HUM00061128). Written informed consent was obtained from all participants or their proxies.

In the current study, we included 17,914 participants aged 51–90 years with available data of ARFIs in 2000 and followed them up until 2020, of whom 57.5% were female and 82.9% were White. We conducted several analyses with different sample sizes (Figure S1): (1) we included participants without each ARFI at baseline to calculate the incidence rates (N = 12,756 participants for visual impairment, 12,974 for hearing impairment, 11,028 for cognitive impairment, 14,346 for physical frailty, 9,671 for restless sleep, and 12,786 for depression); (2) we included 15,852 participants with complete ARFI measurements at baseline to describe the progression of co-existing ARFIs; (3) we included participants without missing values of ARFIs or the corresponding outcome ARFIs at baseline to construct the hazard trajectory network (N = 13,913 when treating visual impairment as the exposure, 14,270 for hearing impairment, 13,609 for cognitive impairment, 15,874 for physical frailty, 10,833 for restless sleep, and 14,247 for depression).

Ethics approval

This HRS was approved by the Institute for Social Research of University of Michigan (IRB Protocol: HUM00061128). Written informed consent was obtained from all participants or proxy. No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study.

METHOD DETAILS

Assessments of age-related functional impairments and ascertainment of mortality

In this study, we selected ARFIs that are measured repeatedly in the HRS for analysis, including visual impairment, hearing impairment, restless sleep, cognitive impairment, physical frailty, and depression. All ARFIs were measured biennially, except for physical frailty measured quadrennially. Visual or hearing impairments were defined as self-rated fair or poor visual or hearing functions.[57] Restless sleep is self-reported as a part of the 8-item Center for Epidemiologic Studies-Depression (CES-D) scale.[60] And the other seven items totaled 7 units, with a total score of $\geq$4/7 indicating depression.[65,66] According to a previous study in the HRS, participants aged $\geq$65 years were physically frail if they met more than two of the Fried criteria: low level of physical activity, exhaustion, slowness, weakness, and weight loss.[58,67] Cognitive function was measured using tests adapted from the Telephone Interview for Cognitive Status (TICS) in a 27-point scale,[59] summing scores from immediate and delayed 10-noun free recall tests (1 point for each), serial 7 subtractions (i.e., subtract 7 from 100 and continue subtracting 7 from each subsequent number for a total of five trials, 1 point for each trial), and backward counting from 20 (2 points). A global cognitive score lower than 12 indicated cognitive impairment.[59] All-cause mortality was ascertained using data linkage from the National Death Index and through interviews with informants or knowledgeable others from baseline through May 2019.

Covariates

We included multiple covariates from interviewer-administered structural questionnaires for confounding adjustments. Sociodemographic factors included age, sex (female/male) defined by self-identity, race (White/Black/Others), body mass index (BMI), and education level (lower than high school/general educational development/high school/some college/college and above). Lifestyle factors included smoking status (never/former/current), driking status (never/former/current), household income, and vigorous physical activity (whether more than three times a week). Health conditions included stroke, cancer, memory-related diseases, and other psychological diseases.

QUANTIFICATION AND STATISTICAL ANALYSIS

Baseline characteristics of the study population were described by birth cohorts (WB, HRS original cohort, CODA, and AHEAD), continuous variables in mean (standard deviation) and categorical variables in number (percentage). Because physical frailty was measured every four years, we calculated the four-year incidence rates (2000–2004) of the six ARFIs by age and sex. Using penalized spline,[68,69] we also examined the linear and nonlinear trend of incidence rates with age. We characterized their co-existing patterns by birth cohorts at baseline using the 'ComplexUpset' package.[62] We used the Sankey diagram to characterize the status transitions of participants from 2000 to 2020 using the 'ggalluvial' package.[63]

To illustrate how the ARFIs are associated with each other, we constructed a hazard trajectory network following a three-step strategy introduced in a previous study.[19] First, we calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) for the directional association of each ARFI with other ARFIs and all-cause mortality using Cox proportional hazard models. The person-time was calculated from the baseline to the first occurrence of outcome of interest, death, or loss-to-follow-up, whichever came first. Models were adjusted for age, sex, BMI, race, education, household income, smoking status, drinking status, and vigorous physical activity at baseline. The associations reaching statistical significance at the Bonferroni-corrected thresholds were carried to the second step, where the estimates were further adjusted for prevalence and incidence of other ARFIs to eliminate indirect associations (i.e., that were confounded or mediated by other ARFIs). The associations remaining statistically significant were considered independent links between ARFIs. Using a directed network graph, we integrated these independent links to form a hazard trajectory network. For example, when assessing the association of visual impairment with cognitive impairment, we first calculated the multivariable-adjusted HR for incident cognitive impairment associated with baseline visual impairment. If the association was statistically significant, we would further adjust the model for prevalence and incidence of other ARFIs (in this case, hearing impairment, physical frailty, restless sleep, and depression, categorized as prevalent, incident, or neither) to test whether the relation of visual impairment to cognitive impairment was independent of other ARFIs. Finally, if the association of visual impairment with cognitive impairment was independent of other ARFIs, it would be shown on the trajectory network as an arrow from visual impairment to cognitive impairment. The hazard trajectory network is based on the longitudinal associations between ARFIs and mortality. For each pair of ARFIs, we performed a survival analysis assigning one ARFI as the exposure and the other as the outcome, and vice versa. The exposure ARFI is measured at baseline and the incidence of the outcome ARFI is documented during follow-up. Therefore, the arrows of in the hazard trajectory network demonstrated whether the exposure ARFI was associated with a subsequent higher risk of the outcome ARFI. Taking visual impairment and cognitive impairment as an example, we measured visual impairment at baseline and assessed its association with incident cognitive impairment, and vice versa. The significant associations will be presented in the hazard trajectory network. Two ARFIs, which were both related to higher risk of the other, were considered to be bidirectionally associated with each other. We further assessed the association of the number of ARFIs with mortality using Cox proportional hazard models. We conducted an exploratory analysis evaluating the associations of dyads of baseline ARFIs (in 2000) with mortality in 2000–2019, adjusted for covariates as in the main analyses and the presence of other ARFIs.

We performed a series of sensitivity analyses. First, we excluded people with prevalent stroke, cancer, memory-related diseases, or other psychological diseases that might directly cause functional changes or mortality. Second, we restricted our analyses to participants with none of the six ARFIs at baseline. Third, we treated all-cause mortality as the competing risk using the Fine & Gray model when assessing the associations between the ARFIs.[70]

All statistical analyses were completed using R 4.2.0. All p-values were two-sided and Bonferroni-corrected $p < 0.05$ was considered an indicator of statistical significance to address multiplicity.