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CO-PRESENCE OF MULTIMORBIDITY AND DISABILITY WITH FRAILTY: AN EXAMINATION OF HETEROGENEITY IN THE FRAIL OLDER POPULATION

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Abstract

Background—Frailty is often associated with multimorbidity and disability.

Objectives—We investigated heterogeneity in the frail older population by characterizing five subpopulations according to quantitative biological markers, multimorbidity and disability, and examined their association with mortality and nursing home admission.

Design—Observational study.

Participants—Participants (n=4,414) were from the population-based Age Gene/Environment Susceptibility Reykjavik Study.

Measurements—Frailty was defined by ≥ 3 of five characteristics: weight loss, weakness, reduced energy levels, slowness and physical inactivity. Multimorbidity was assessed using a simple disease count, based on 13 prevalent conditions. Disability was assessed by five activities of daily living; participants who had difficulty with one or more tasks were considered disabled. Differences among frail subpopulations were based on the co-presence of multimorbidity and disability. Differences among the following subpopulations were examined: 1) Non-frail (reference group); 2) Frail only; 3) Frail with disability; 4) Frailty with multimorbidity; 5) Frail with disability and multimorbidity.

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Conflict of interest: There are no conflicts of interest to declare

Ethical standards: AGES-Reykjavik was approved by the National Bioethics Committee in Iceland that acts as the institutional review board for the IHA and by the National Institute on Aging's Institutional Review Board.

Results—Frailty was present in 10.7% (n=473). Frailty was associated with increased risk for mortality (OR 1.40; 95% CI 1.15–1.69) and nursing home admission (OR 1.50; 95% CI 1.16–1.93); risks differed by subpopulations. Compared to the non-frail, the frail only group had poorer cognition and increased inflammation levels but did not have increased risk for mortality (OR 1.40; 95% CI 0.84–2.33) or nursing home admission (OR 1.01; 95% CI 0.46–2.21). Compared to the non-frail, the other frail subpopulations had significantly poorer cognition, increased inflammation levels, more white matter lesions, higher levels of calcium, glucose and red cell distribution width and increased risk for mortality and nursing home admission.

Conclusions—The adverse health risks associated with frailty in the general older adult population may primarily be driven by increased disease burden and disability.

Keywords

Frailty; comorbidity; disability; community-dwelling; multimorbidity; disease

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Frailty is described as a state of increased vulnerability that may result from decreased physiological reserve, multisystem dysregulation and diminished capacity to maintain homeostasis (1). The prevalence of frailty depends on the operational definition used and source population; although consensus has been reached regarding the domains on which frailty should be assessed, there is still no agreement among experts regarding the diagnostic paths and procedures for an operational definition of frailty (2). Consequently, frailty is sometimes still used interchangeably with other geriatric conditions, such as multimorbidity and disability and is still operationalized in various manners (3, 4). However, all studies on frailty demonstrate that frailty increases with advancing age (4). For example, the overall prevalence of frailty among 5,317 community-dwelling older adults participating in the Cardiovascular Health Study was 6.9%, but in participants who were 80 and older the prevalence was 30% (4). Frailty is known to increase the risk for a variety of adverse health outcomes including hospitalization (5), disability (6) and mortality (7–9), which may exert a high burden on health care systems.

Previous research suggests that frailty not only exists independent of age-associated diseases, but could also contribute, for example, to the incidence and progression of multimorbidity, disability and mortality (4). Moreover, frailty and multimorbidity are, to date, both known to be independent risk factors for disability (2). Disability in turn, may exacerbate the health related problems associated with frailty and multimorbidity. Hence, the three conditions are interrelated but the degree of mutual dependence is not well established. While previous studies have examined the effect of frailty on mortality and nursing home admission adjusting for the presence of disability and multimorbidity, no studies have characterized the co-occurrence of frailty with disability and multimorbidity in relation to health outcomes. Therefore, it remains unclear whether the risks for adverse outcomes associated with frailty are driven by disease burden (10), including possibly subclinical diseases and impairments that may underlie frailty.

Given the correlation between frailty, multimorbidity and disability, we sought to investigate heterogeneity within the frail population in a large cohort of community-dwelling older adults. The first aim was to estimate the overall prevalence of frailty in community dwelling

older adults as well as to estimate the co-presence of disability and multimorbidity within the frail population. The second aim was to characterize subpopulations of frail older adults with quantitative physiological markers. Since the risk of adverse outcomes may differ per subpopulation of frailty, the last aim was to examine the risk for mortality and nursing home admission in subpopulations of frail and non-frail older adults.

Methods

Study Population

The Age Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) Study is based on the Reykjavik Study, a population-based cohort established in 1967 by investigators at the Icelandic Heart Association (IHA) (11, 12). This cohort originally comprised a random sample of men and women born between 1907 and 1935 and living in Reykjavik at baseline. The initial follow-up examination for AGES-Reykjavik started in 2002 and was completed in 2006 (13). As part of the AGES-Reykjavik Study, participants (n=5,764) completed interviews about a variety of health related factors, including functional status, medical conditions, health behaviors, and family history. Moreover, participants had a series of standardized health examinations. AGES-Reykjavik was approved by the National Bioethics Committee in Iceland that acts as the institutional review board for the IHA and by the National Institute on Aging's Institutional Review Board. Release of data for analysis is governed by rules created by these bodies to protect the privacy of Icelandic participants (13). Participants with Parkinson's disease (i.e. their symptoms and functional impairments would interfere significantly with the frailty assessment), participants who had not undertaken an MRI scan (which might have been due to the physical status of the participant) or had missing data on the variables on which the subpopulations of the current study were based (i.e. frailty characteristics, multimorbidity and disability) were excluded (n=1,350; 23.4%). People who were excluded were older and less educated than those included in the analysis. There was no difference in sex distribution. The final analytic study sample yielded 4,414 participants.

Assessment of Frailty

The present study used the most frequently used operational definition of frailty developed by Fried and colleagues (8, 14). The phenotype of frailty was identified by the presence of three or more of the following characteristics (8):

1. Weight loss: unintentional weight loss of 5 kg or more in the past 12 months or a Body Mass Index (BMI) less than 18.5 kg/m^2.
2. Weakness: hand grip strength in the lowest 20% adjusted for height and sex.
3. Low energy: reduced energy level determined by the respondent answering 'no' to 'Do you feel full of energy?' in the Geriatric Depression Scale.
4. Slowness: slowest 20% of the study population, based on usual gait speed over a 6-meter course, adjusted for height and sex.

5. Low physical activity: no swimming or walking during the summer and winter season and no participation in low and moderate/vigorous physical activity during the last 12 months.

Assessment of Disability

Difficulty in carrying out activities of daily living (i.e. walking from one room to another, getting in and out of bed, eating, dressing and showering/bathing) were assessed by five questions (15). Each question had a 4-point Likert response: 1) 'no difficulty', 2) 'some difficulty', 3) 'much difficulty', and 4) 'I am unable to do it'. Participants who had difficulty with at least one ADL task (i.e. a score of 2 or more on one of the five questions) were considered disabled.

Assessment of Multimorbidity

Multimorbidity was defined as the co-occurrence of two or more diseases (16) and was quantified by counting the number of diseases (17) (see Appendix). Anemia was defined based on the World Health Organization criteria of hemoglobin concentration of <12g/dL in women and <13g/dL in men. Chronic Kidney Disease was defined by using an estimated glomerular filtration rate of less than 60mL/min/1.73m2 calculated by the Modification of Diet in Renal Disease (MDRD) (18). Diabetes was defined as a history of diabetes, use of glucose-modifying medication, or fasting blood glucose of >7 mmol/L. Coronary Heart Disease and angina pectoris were both based on electrocardiograms and questionnaire (19). To diagnose dementia cases, participants were screened using the Mini-Mental State Examination and the Digit Symbol Substitution Test (21), were administered a diagnostic battery of neuropsychological tests and were examined by a neurologist. A consensus diagnosis of dementia, according to international guidelines, was made by a panel that included a geriatrician, neurologist, neuropsychologist and neuroradiologist. The remaining medical conditions were based on the AGES health questionnaire. All questions related to these medical conditions were formulated in the same manner (e.g. 'Has a doctor or other health professional ever told you that you had cancer?'). The answer 'I don't know' was assigned a missing value.

Frailty Groups

The following four subpopulations of participants with frailty were examined: 1) 'Only frail' (no disability or multimorbidity); 2), 'Frail with disability' (FD; no multimorbidity); 3) 'Frail with multimorbidity' (FM; no disability), and 4) 'Frail with disability and multimorbidity (FDM). For all analyses, the non-frail participants, who did not meet frailty criteria, served as the reference group.

Assessment of Markers of Physiological Dysfunction

The following quantitative markers which are known to reflect disease burden and/or subclinical impairment were examined: White matter hyperintensities (WMH) were assessed by MRI and divided by total intracranial volume. The presence of brain infarcts was identified as defects in the brain parenchyma with hyperintensities on T2 and FLAIR images with a maximal diameter of at least 4mm (21). Glucose levels were determined by a fasting

morning blood draw. Coronary artery calcium level (CAC) was quantified by summing all 4 coronary arteries according to the Agatston method (22, 23). Estimated Glomerular Filtration Rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula (18). The red cell distribution width (RDW) was reported as part of the complete blood count, (24). C-Reactive Protein (CRP) was measured on a Hitachi 912, using reagents from Roche Diagnostics (25). Bone Mineral Density was assessed by the amount of bone matter per cubic cm (26). Composite scores for speed of processing, memory and executive functioning were constructed (details have been described elsewhere (27).

Assessment of Mortality and Nursing Home Admission

Every participant was followed until 31, May 2010 for mortality and nursing home admission. Mean follow-up was 5.94 (SD: 1.22) years for nursing home admission and 7.76 (SD: 1.44) for mortality. Mortality information is provided by Statistics Iceland (www.statice.is). Information on nursing home admission stems from the Inter Resident Assessment Instrument (InterRAI) (28).

Statistical Analysis

Linear and logistic regression analyses, adjusted for age and sex, were used to determine differences in quantitative disease markers by subpopulations of frailty. Cox proportional hazards models were used to determine the association of frailty status with mortality and incident nursing home admission. The first model was adjusted for age and sex only, while the second model was adjusted for age at time of examination, sex, education (high vs. low education; primary and secondary school vs. college and university), smoking status (never smoked, former smoker and current smoker), alcohol intake (grams of alcohol per week), living arrangement (living alone vs. living together), and depressive symptoms (assessed by the 15-item Geriatric Depression Scale), all included diseases and total disease count. Hazard ratios (HR) and 95% confidence intervals (CI) are reported. P-values of 0.05 or less were considered statistically significant. Statistical analyses were conducted using the SPSS statistical software package version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Figure 1 illustrates the co-occurrence of frailty, disability and multimorbidity. The overall prevalence of frailty was 10.7% (n=473). A total of 4.3% (n= 190) of older adults had frailty, disability and multimorbidity, while 2.1% (n= 94) were frail and disabled and 2.8% (n= 125) had frailty and multimorbidity. Among frail participants, 40.1% (n=190) had disability and multimorbidity. Although the majority of frail participants reported ADL disability and/or multimorbidity, 13.5% (n=64) was ‘only frail’ (i.e. did not report ADL disability and did not have any of the condition used to assess multimorbidity).

Descriptive characteristics of the 4,414 participants are shown in Table 1. The average age was 76.4 years and 57.4% (n=2,532) were female. In general, frailty characteristics were similarly distributed across the frail subpopulations; however, the weight loss criterion was more common in the ‘only frail’ group compared with the other frail subpopulations (Table 2).

After adjusting for age and sex, several quantitative markers of disease burden and functional impairment were significantly associated with ‘only frail’ status (Table 3). Participants who were ‘only frail’ had decreased memory function, processing speed and executive function and had higher CRP values compared with non-frail participants. There was no difference between these two groups in terms of white matter lesions and brain infarcts as well as no differences in BMD, CAC, eGFR, glucose level and RDW. The other three frail subpopulations (FD, FM and FDM) had poorer neurocognitive performance than the non-frail group, but also higher white matter lesions, CAC, and RDW values. No differences in BMD or eGFR were observed in these groups.

Frail older adults were approximately 2-times more likely to die or be admitted to a nursing home compared with non-frail participants, adjusting for age and sex (Model 1, Table 4). The effect of frailty on each outcome remained statistically significant after further adjusting for confounding factors although the effect sizes were attenuated (Model 2).

Table 5 shows the relative risks for mortality and nursing home admission according to frail subpopulations. Compared with non-frail older adults, frail participants with multimorbidity (FM and FDM subpopulations) had a significantly increased risk for mortality; however, those who were ‘only frail’ and those with frailty and disability (FD) did not have an increased mortality risk. In addition, the ‘only frail’ subpopulation without disability and multimorbidity did not have an increased risk for nursing home admission compared with non-frail participants. In contrast, frail participants with disability and frail participants with frailty, disability and multimorbidity were significantly more likely to be admitted to a nursing home compared with non-frail older participants.

Discussion

The present study, conducted in a large population-based sample of older adults, sought to investigate the heterogeneity within the frail population by examining subpopulations of frailty. The present study shows that, although frailty is often accompanied by multimorbidity and disability, 13.5% of all frail people appeared to be ‘only frail’ (i.e. frail without the presence of multimorbidity and/or disability); this percentage is comparable to a recent conducted study which reported 12.6% to be frail alone (9). Apart from weight loss, which was more apparent in the ‘only frail’ group, in general, the frailty characteristics were evenly distributed across the frail subpopulations. Compared with non-frail participants, the ‘only frail’ subgroup had significantly lower cognitive function and higher levels of CRP. Our findings not only underscore that frailty can exist without the presence of multimorbidity and disability but also suggest, in congruence with previous research (4, 9), that frailty can result from age related physiologic changes that are not disease or disability based. The other three subpopulations of frailty not only showed a decrease in neurocognitive performance and elevated inflammation values, but were also associated with higher levels of white matter lesions (the FD and FDM group), CAC (i.e. the FM and FDM group) and RDW values (i.e. the FM and FDM group).

In a recent study, mortality risk only increased when frailty, multimorbidity and disability (i.e. reported as ‘dependency’) were combined (9). Our results underscore that frailty perse

is not a predictor of mortality; the 'only frail' group was not at an increased risk of mortality and nursing home admission. In addition, while the FM and FDM group had an increased risk for mortality; the FD and FDM group had an increased risk for nursing home admission. Our results also pinpoint, that multimorbidity and disability alone, are related to adverse health outcomes such as nursing home admission and mortality.

The present results indicate that although frailty is often accompanied by multimorbidity and disability, a substantial portion of older individuals are frail without having multimorbidity and/or disability. Our results are in congruence with a study by Fried and colleagues which claimed that frailty is not synonymous with either the presence of chronic diseases or disability (4). A study by Fried and colleagues showed that 27% of the participants were frail without having comorbid diseases and ADL disability, while 21.5% of participants were frail with multimorbidity and ADL disability [8]. In the present study, these percentages were respectively 13.5% and 40.1%. The dissimilarity in prevalence estimates between the present study and the study conducted by Fried and colleagues could be due to differences regarding the assessment of frailty, ADL disability and multimorbidity. For example, while the study by Fried and colleagues used a more elaborate index to assess ADL disability, our study used a more complete nosological spectrum to assess multimorbidity. Moreover, the abovementioned difference in obtained prevalence estimates may also be explained by the difference in populations under study (i.e. Icelandic population and Americans from European and African descent)

Cognitive functioning, as assessed by memory function, processing speed and executive function, was significantly decreased in all frail subpopulations as compared with non-frail participants. White matter hyperintensities were only related to subpopulations of frailty in which ADL disability was present (i.e. FD and FDM group). Previous evidence suggest that frailty is not only associated with cognitive decline but also with Alzheimer pathology on postmortem examination (29). The mechanism through which neurocognitive dysfunction plays a role in frailty has not yet been defined. It is speculated that accumulation of Alzheimer pathology could affect components of frailty by impairing neural systems involved in planning and monitoring physical functioning (29). Compared to the non-frail, the presence of brain infarcts was much higher in all subpopulations of frailty. Nevertheless, no significant association between brain infarcts and frail subgroups were detected. A study by Newman, based on the Cardiovascular Health study, illustrated that there is significant association between frailty and cerebral infarcts (10). This difference in obtained effects might be due to the fact that the present study investigated subpopulation of frailty while Newman and colleagues investigate different stages of frailty (i.e. nonfrail, intermediate frail and frail).

Interestingly, the frail subpopulations with multimorbidity (i.e. the FM and FDM group) showed elevated CAC levels. Although frailty has been associated with cardiovascular disease related outcomes (10), the present results indicate that elevated CAC levels are not associated with frailty per se, but merely with the co-presence of diseases. The present study also provides evidence for the relation between inflammation and frailty, since elevated CRP levels appear to be present in all frail subpopulations. Recent evidence suggests that frailty is not related to one deficient dominant deregulated system (e.g. inflammation) but is

associated with the total number of abnormal physiological systems (30). Consequently, frailty has been suggested to be a nonlinear complex system that is independent of any specific system abnormalities (2, 30). Our results provide evidence for this postulation since various quantitative markers, such as CRP, RDW and fasting glucose (31) all appear to be associated with frailty. The mechanism by which these impairments influence frailty still remains to be determined.

When evaluating the risk of mortality and nursing home admission for different frail subpopulations, our results indicate that, while mortality seems primarily driven by disease burden, functional limitations seem to be the driving force behind nursing home admission. Hence, the absence of multimorbidity and disability in the 'only frail' seems to lower their risk for mortality and nursing home admission.

The current study does have some limitations that should be considered. Several medical conditions and disability were based on participants' self-reports, which could have compromised the validity of these data. Although self-reported disease status has been shown to correlate reasonably well with medical records, the oldest old (i.e. people aged 90 and over) tend to under-report certain diagnosed medical conditions (32). Moreover, the present study included thirteen highly prevalent medical conditions, all well known for their profound negative effects on health. Nevertheless, other medical conditions that were not evaluated could not only have underestimated the prevalence of multimorbidity, but could also underlie some of our findings. Participants with one or more missing frailty characteristics were included in the present study, which could resulted in an overrepresentation of 'healthy' participants. This 'survivor effect' may have led to an underestimations of the associations obtained in this study. In addition, because of the small sample size of frail subpopulations, the current study could have lacked power to, for example, detect an increased risk of mortality and nursing home admission for 'only frail' participants. However, since the confidence intervals of all survival analysis are rather small, it is not likely that a lack of power comprised our results. In addition, the current study did not assess cognition for the assessment of frailty, as has been recently suggested by several expert in the field (2). The current study did use the most frequently used operationalization of frailty by including domains such as energy, physical activity and strength. Hence, future research should establish if similar results are found when cognition is included as a 'frailty domain'.

In summary, the present study indicates that heterogeneity within the frail populations should not be ignored. Heterogeneity in the frail older adult population present a challenge to understanding whether frailty is a reflection of disease burden or disability or is a true underlying state of vulnerability. The current study identified a subpopulation of older adults ('only frail') who were not at an increased risk for mortality or nursing home admission, but that did display decreased neurocognitive performance and increased CRP levels. Although this subpopulation of frailty appears small, this group will be of use in order to further investigate the pathogenesis of frailty and frail subpopulations. In addition, when, in due time, consensus on an operational definition of frailty has been reached, the present study could be repeated in order to provide a more thorough understanding of frailty and its relation to adverse health outcomes.

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Appendix

Prevalence (percentages) of medical conditions included in the present study

	Nonfrail (n=3,941)	Only Frail (n=64)	FD (n=94)	FM (n=125)	FDM (n=190)
Diabetes	451 (11.4)	4 (6.3)	6 (6.4)	18 (14.4)	44 (23.2)
Dementia	150 (3.8)	3 (4.7)	9 (9.6)	20 (16.0)	38 (20.0)
Anemia	280 (7.1)	3 (4.7)	2 (2.1)	35 (28.0)	46 (24.2)
Osteoporosis	78 (2.0)	0	1 (1.1)	3 (2.4)	11 (5.8)
Arthritis	1,440 (36.5)	13 (20.3)	27 (28.7)	68 (54.4)	106 (55.8)
Cancer	493 (12.5)	4 (6.3)	7 (7.4)	31 (24.8)	51(26.8)
Coronary Heart Disease	805 (20.4)	5 (7.8)	6 (6.4)	41 (32.8)	68 (35.8)
Kidney disease	1,142 (29.0)	7 (10.9)	3 (3.2)	76 (60.8)	101 (53.2)
Liver disease	54 (1.4)	1 (1.6)	2 (2.1)	3 (2.4)	0
Fractures (pelvis/hip)	86 (2.2)	1 (1.6)	0	6 (4.8)	14 (7.4)
Asthma	532 (3.1)	3 (4.7)	2 (2.1)	24	45 (23.7)
COPD	123 (3.1)	0	2 (2.1)	6 (4.8)	16 (8.4)
Stroke	197 (5.0)	3 (4.7)	2 (2.1)	17 (13.6)	34 (17.9)

FD: Frail and Disability; FM: Frail and Multimorbidity; FDM: Frail, Disability and Multimorbidity. Results are presented as n (percentages)

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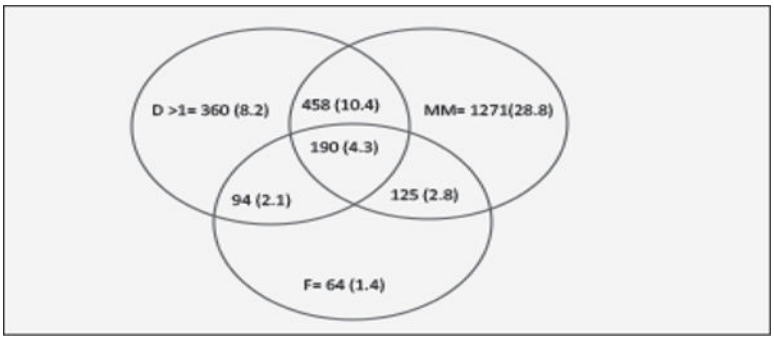

Figure 1. Venn diagram displaying the overlap in prevalence (%) between frailty, multimorbidity and disability

F=’only frail’, D=Disability, MM=Multimorbidity; Total n=4,414; healthy n=1,852 (42.0%; i.e. no frailty, multimorbidity or disability).

Table 1

Characteristics of study population by frailty status and subpopulations

	Nonfrail (n=3,941)	Only Frail (n=64)	Frail and disability (n=94)	Frail and multimorbidity (n=125)	Frail and disability and multimorbidity (n=190)	Total (n=4,414)
Age in years (SD)	76.0 (5.3)	80.0 (4.7)	80.7 (5.3)	80.5 (5.6)	79.9 (5.7)	76.4 (5.5)
Sex (% women)	2,262 (57.4)	31 (48.4)	50 (53.2)	75 (60.0)	114 (60.0)	2,532 (57.4)
Education (% high)	463 (11.7)	4 (6.3)	8 (8.5)	11 (8.8)	14 (7.4)	500 (11.3)
Living alone (%)	1,397 (35.4)	26 (40.6)	38 (40.4)	62 (49.6)	97 (51.1)	1,620 (36.7)
Smoker (%)						
Never smoked	1,663 (42.2)	24 (37.5)	41 (43.6)	60 (48.0)	75 (39.5)	1,863 (42.2)
Former smoker	1,801 (45.7)	27 (42.2)	41 (43.6)	48 (38.4)	87 (45.8)	2,004 (45.4)
Current smoker	477 (12.1)	13 (20.3)	12 (12.8)	17 (13.6)	28 (14.7)	547 (12.4)
Alcohol (SD)	15.1 (32.0)	10.9 (21.7)	14.4(38.8)	16(47.8)	11.6 (31.7)	14.9 (32.6)
ADL (% ≥ 1)	818 (20.8)	0	94 (100)	0	190 (100)	1,102 (25.0)
GDS score (SD)	2.1 (1.9)	3.7 (2.0)	3.8 (2.2)	3.5 (1.8)	4.4 (2.8)	2.3 (2.0)
Disease count (%)						
0	875 (22.2)	17 (26.6)	25 (26.6)	0	0	917 (20.8)
1	1,337 (33.9)	47 (73.4)	69 (73.4)	0	0	1,453 (32.9)
2	1,003 (25.5)	0	0	60 (48.0)	76 (40.0)	1,139 (25.8)
≥ 3	726 (18.4)	0	0	65 (52.0)	114 (60.0)	905 (20.5)

Age, Alcohol and GDS score are reported as means (SD). ADL was assessed as a score of 2 or more on one of the five questions) GDS (i.e. Geriatric depression Scale) score was assessed using 15 items; a total score of 6 or more is indicative for a plausible depression; Alcohol consumption was assessed by the days of alcohol consumption per months, converted into grams of alcohol per month (using 14 g of alcohol as standard drink). Finally, this was divided by 4.35 (4.35 weeks in a month). Disease count (i.e. total number of diseases); diabetes, dementia, anemia, osteoporosis,, arthritis, cancer, coronary heart disease, kidney disease, liver disease, history of fractures (pelvis/hip), asthma, COPD, and stroke.

Table 2

Prevalence (percentages) of frailty characteristics

	Nonfrail (n=3,941)	Only Frail (n=64)	Frail and disability (n=94)	Frail and multimorbidity (n=125)	Frail and disability and multimorbidity (n=190)	Total (n=4,414)
Low energy	1,798 (45.6)	62 (96.9)	89 (94.7)	121 (96.8)	184 (97.0)	2,254 (51.1)
Low physical activity	345 (8.8)	32 (50.0)	55 (58.5)	56 (44.8)	107 (56.3)	595 (13.5)
Weakness	512 (13.0)	46 (71.9)	64 (68.1)	95 (76.0)	125 (65.8)	842 (19.1)
Weight loss	127 (3.2)	20 (31.2)	12 (12.8)	27 (21.6)	37 (19.5)	223 (5.1)
Slowness	435 (11.0)	44 (68.8)	79 (84.0)	95 (76.0)	167 (87.9)	820 (18.6)
Mean (SD) *	0.82 (0.74)	3.19 (0.39)	3.18 (0.39)	3.15 (0.38)	3.26 (0.48)	1.07 (1.03)

* Mean number of frailty characteristics.

Table 3

Age and sex adjusted means (95% confidence interval) and prevalence (percentages) of quantitative markers of disease burden and functional impairment

	Non-frail (n=3,941)	Only Frail (n=64)	Frail with disability (n=94)	Frail and multimorbidity (n=125)	Frail with disability and multimorbidity (n=190)
Neurological					
Memory	0.04 (0.01, 0.07)	−0.24 (−0.46, −0.1)†	−0.30 (−0.49, −0.11)†	−0.42 (−0.58, −0.26)†	−0.27 (−0.40, −0.14)†
Processing speed	0.05 (0.02, 0.08)	−0.45 (−0.68, −0.23)†	−0.35 (−0.53, −0.16)†	−0.32 (−0.48, −0.16)†	−0.50 (−0.63, −0.37)†
Executive function	0.05 (0.02, 0.08)	−0.15 (−0.38, −0.08)*	−0.34 (−0.53, −0.15)†	−0.33 (−0.50, −0.17)†	−0.56 (−0.69, −0.42)†
White matter lesions	1.31 (1.26, 1.35)	1.49 (1.13, 1.84)	1.69 (1.41, 1.98)*	1.55 (1.29, 1.80)	1.90 (1.69, 2.10)†
Brain infarct (%)	1,039 (26.4)	21 (32.8)	33 (35.1)	40 (32.0)	67 (35.3)
Musculoskeletal					
Bone Mineral Density	0.18 (0.18, 0.19)	0.18 (0.17, 0.18)	0.19 (0.18, 0.19)	0.19 (0.17, 0.19)	0.19 (0.18, 0.20)
Cardiac					
CAC	678 (647, 709)	674 (430, 918)	568 (366, 771)	958 (784, 1,132)†	1,065 (923, 1,208)†
Metabolic and other					
eGFR	68.5 (68.0, 69.0)	79.9 (75.8, 84.0)	81.1 (77.7, 84.5)	62.8 (59.9, 65.7)	62.6 (60.2, 64.9)
Glucose	103.9 (103.3, 104.6)	100.7 (95.7, 105.8)	103.7 (99.5, 107.9)	104.8 (101.2, 108.5)	107.4 (104.5, 110.4)*
C-reactive protein	3.41 (3.21, 3.60)	4.82 (3.26, 6.38)*	5.10 (3.80, 6.39)*	6.38 (5.26, 7.51)†	5.94 (5.03, 6.85)†
RDW	13.0 (12.9, 13.0)	13.1 (12.9, 13.4)	13.2 (13.0, 13.4)	13.3 (13.1, 13.4)†	13.4 (13.2, 13.5)†

The variables memory, speed and executive functioning are composite, standardized scores with mean 0 and standard dev of 1 in the total population. Brain infarcts are reported using prevalence estimates and corresponding percentages; CAC: Coronary artery calcium level; eGFR: Estimated Glomerular Filtration Rate, RDW: Red cell Distribution Width; The reference group consisted of non-frail participants:

*p ≤0.05;

†p ≤0.01

Table 4

Mortality and nursing home admission according to frailty status

	# events (% within group)	Event rate per 1000 person-years	Model 1 HR (95%CI)	Model 2 HR (95%CI)
Mortality				
Nonfrail	656 (16.6)	29	1.00	1.00
Frail	191 (40.3)	79	1.86 (1.57 – 2.21)	1.40 (1.15 – 1.69)
Nursing home admission				
Nonfrail	280 (7.1)	12	1.00	1.00
Frail	123 (26.5)	48	2.33 (1.86 – 2.91)	1.50 (1.16 – 1.93)

The reference groups consist of non-frail participants. HR: Hazard Ratio; CI: Confidence Interval

Table 5

Mortality and nursing home admission in frail subpopulations

	# events (% within group)	Event rate per 1000 person-years	Model 1 HR (95%CI)	Model 2 HR (95%CI)
Mortality				
Nonfrail	656 (16.6)	29	1.00	1.00
Only frail	18 (28.1)	52	1.24 (0.78–1.99)	1.40 (0.84 – 2.33)
FD	27 (48.7)	54	1.14 (0.78–1.69)	1.20 (0.75 – 1.92)
FM	56 (44.8)	90	2.10 (1.59–2.78)	1.47 (1.09 – 1.99)
FDM	89 (46.8)	94	2.37 (1.89–2.98)	1.42 (1.09 – 1.84)
Nursing home admission				
Nonfrail	280 (7.1)	12	1.00	1.00
Only frail	8 (12.9)	22	1.13 (0.56–2.29)	1.01 (0.46 – 2.21)
FD	28 (30.4)	59	2.80 (1.91–4.20)	2.00 (1.20 – 3.33)
FM	32 (26.4)	46	2.10 (1.47–3.10)	1.47 (0.98 – 2.21)
FDM	54 (28.7)	53	2.65 (1.96–3.58)	1.45 (1.02 – 2.06)

The reference groups consist of non-frail participants. FD: Frail and Disability; FM: Frail and Multimorbidity; FDM: Frail, Disability and Multimorbidity; HR: Hazard Ratio; CI: Confidence Interval; Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, education, smoking status, alcohol intake, living arrangements, disability, depressive symptoms, all included diseases and disease count.