Frailty Transitions in Community-Dwelling Older People
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ABSTRACT: Background: Frailty is a dynamic process with transitions over time. Objectives: To examine frailty transitions and their relationship to utilization of health services. Methods: Frailty status using the Vulnerable Elders Survey (VES-13) was determined for 608 community-dwelling older people interviewed in a 2008 national survey and for 281 re-interviewed in 2014. The effect of frailty on death 6 years later was assessed using Cox proportional hazards analysis. Participants were divided into four groups based on their frailty transition. Demographic, functional and health characteristics were compared between the four groups using the Kruskal-Wallis and paired t-test. The independent association between the four frailty groups and health services utilization was assessed using logistic regression. Results: Between 2008 and 2014, 24% of 608 participants were lost to follow-up, 9% were non-frail, 37% were frail, and 30% died. The Cox ratio showed that 86% of the non-frail in 2008 were alive 6 years later vs. 52% of the frail (hazard ratio 3.5, confidence interval 2.2–5.4). Frailty transitions in the 281 participants interviewed at both time points revealed that 19% stayed non-frail, 22% became frail, 22% stayed frail and 37% became more frail. Becoming frail, staying frail or becoming more frail compared to staying non-frail was independently associated with a greater risk for requiring help on a regular basis, having a formal caregiver, and requiring home care. Conclusions: Any transition away from the non-frail state increased the use of health care services. Interventions to target early transition to frailty should be encouraged.

KEY WORDS: frailty, Vulnerable Elders Survey (VES-13), health services utilization, aging, transition

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Frailty is recognized as a geriatric syndrome that is characterized by increased risk for adverse outcomes such as functional decline, hospitalization, and death due to abnormalities in multiple physiological systems [1-3]. Frailty is not synonymous with disability or co-morbidity but helps us describe the heterogeneity of the elderly population. In addition, frailty can help us identify populations at risk in order to design effective interventions to prevent adverse outcomes and increased health services utilization. In a population of elderly admitted for elective surgery, frailty was found to predict postoperative complications, longer length of stay and nursing home placement better than traditional predictive tools [4]. A recent study has shown that the progression to frailty in older people identified as pre-frail can be prevented with exercise [5]. Finally, frailty can help us in clinical decision making. For example, the approach to treating hypertension will be different if the older person is robust rather than frail [6].

Many models have been developed to identify and define frailty [7]. The two major approaches are the phenotype of frailty developed by Fried et al. [2] which is based on data from the Cardiovascular Health Study, and the accumulation of deficits model of Rockwood et al. [8] that is based on the assumption that the more systems go wrong in the body the more likely a person is to be frail [8]. However, these two indices are quite difficult to operationalize. A third approach is the Vulnerable Elders Survey (VES-13) developed by Saliba and co-researchers [9]. This is a simple to administer 13-question function-based survey [10]. A score of ≥ 3 defines “vulnerability,” a term consistent with frailty, and predicts a 4.2 times increased risk for death or functional decline within 2 years. Vulnerability status predicts mortality, functional decline and increased health service utilization [11]. In addition, it has been shown that higher VES-13 scores indicate greater vulnerability and risk of adverse outcomes [12]. It has been recommended that the VES-13 be used as a screening tool to identify frail older people appropriate for comprehensive geriatric assessment [13].

Gill et al. [14], in an innovative study, have shown that frailty is a dynamic process and that older people were more likely to transition from non-frail to frail and to states of greater frailty over time. The rate of transition from frail to non-frail was very small. He concluded that given the dynamic nature of frailty, ample opportunities for intervention exist to prevent or remediate frailty. Another study that examined transitions was the Women's Health and Aging Study II (WHAS II), where 72% of the women had at least one transition between frailty states in 7.5 years [15].

Understanding transitions in frailty states is important for clarifying the natural history of frailty. Designing interventions to prevent or treat frailty is dependent on understanding this
narrow transitions from a robust state to a pre-frail state or from a frail state to a more frail state will help us identify when and how to intervene to prevent the transition to a worse state. Studies on frailty and especially on frailty transitions have not been done in Israel. The two Israeli longitudinal studies of older people did not include frailty as a variable [16,17]. Therefore, in order to learn about the transitions that frail and robust older people undergo over time we undertook a follow-up study of a national survey on community-dwelling older people. Our objectives were to examine frailty transitions and the impact of these transitions on function and health services utilization.

PATIENTS AND METHODS
This follow-up study was drawn from a sample population of 608 community-dwelling older people age 65 and over who were members of Maccabi Healthcare Services, the second largest health fund in Israel with a membership of two million. These older people were screened for frailty in 2008 using the Vulnerable Elders Survey (VES-13) as part of a national study of community-based comprehensive geriatric assessment (CGA) [18]. These 608 participants were drawn consecutively from the four regional CGA clinics, and from a random sample drawn from one region where Maccabi did not have a CGA clinic. In the 2008 screening, 74% (N=447) were found to be frail (VES-13 score ≥ 3). Six years later, in 2014, the participants were contacted again. Names and identification numbers were matched with the administrative databases to identify older people who had died (N=183, 30%). Trained interviewers then contacted the 425 surviving older people (70%); of these, 144 (24%) were lost to follow-up: the telephone number was wrong in 13%, 6% refused, 2% were in a nursing home, and 3% for other reasons. Those who were lost to follow-up did not differ significantly from the participants (those who died and those who were interviewed) in terms of age, gender, marital status, country of origin, education level, living alone, or baseline VES-13 score. Thus, 281 older people (46%) were interviewed in 2014 to determine their utilization of health services, functional status and VES-13 score. Eighty-five interviews (30%) were conducted with a proxy respondent. The research protocol was approved by the institutional review board of the participating health fund (no. 2013088).

TOOLS
The Vulnerable Elders Survey (VES-13) is a simple 13-item screening tool that asks older people to report their age, their ability to perform six physical and five functional activities, and their self-rated health. It aims to identify a group of community-dwelling older people at risk for death or decline who might therefore benefit from improved detection and care of prevalent medical and geriatric conditions known to result in functional decline and mortality. Non-clinical personnel can administer the VES-13 during a brief (5 minute) telephone interview and derive a score ranging from 0 (lowest risk) to 10 (highest risk) [10]. Using Medicare Current Beneficiary Survey (MCBS) data, one study found that VES-13 scores of ≥ 3 identified a group of older people at 4.2 times greater risk of functional decline or death within 2 years than those with scores < 3 (49.5% vs. 11.8%) [9]. The addition of co-morbidity variables to the VES-13 scale was assessed by Saliba et al. [9] and did not improve the validity and reliability of the tool.

VARIABLES
The main outcome variables were frailty status (non-frail, frail) as measured by the VES-13 scale in 2008 and in 2014, and death. Cognitive status was measured by the question “have you noticed that in the past year you have had problems with your memory?” Functional status was measured using the Barthel 0–20 questionnaire [19]. Other functional parameters included fall status in the past year, whether the participant engaged in physical activity at least once a week, and the question “do you need help on a regular basis?” Variables relating to health services utilization included hospitalization in the past year, emergency room (ER) visit in the past year, presence of a paid formal caregiver, having had a comprehensive geriatric assessment in the past 3 years, and being enrolled in the homecare program.

STATISTICAL ANALYSIS
Subjects were divided into four groups based on the transition that occurred between 2008 and 2014 as measured by the difference in the VES-13 score at these two time points. To compare demographic, functional and health characteristics between the four groups of frailty, the Kruskal-Wallis test was performed to compare categorical differences and paired t-test for continuous variables. Logistic regression was performed to determine the independent association between the four frailty groups and health service utilization (hospitalization, ER visit, home care, presence of a paid caregiver).

To evaluate mortality effects in the full sample of 608 older people, a Cox proportional hazards survival analysis was performed to determine the effect of the VES-13 score on death at 6 years.

RESULTS
The mean baseline VES-13 score in 2008 for the group identified as non-frail (n=161, 26%) was 1.1 ± 0.7 (range 0–2) and for those identified as frail (n=447, 74%) as 7.0 ± 2.1 (range 3–10). The mean age of patients at baseline was 79 ± 7 years, and two-thirds were female.

Of 161 subjects identified as non-frail in 2008, the 2014 reassessment revealed that 30% (N=48) remained non-frail,
39% (N=63) became frail, 14% (N=23) had died and 17% (N=27) were lost to follow-up. Of 447 subjects identified as frail in 2008, 1% (N=6) became non-frail in 2014, 37% (N=167) remained frail, 36% (N=160) had died, and 26% (N=117) were lost to follow-up [Table 1]. Thus, incident frailty between 2008 and 2014 was 39%. There were a total of 252 transitions between the groups non-frail, frail and death. The Cox ratio showed that 86% of the non-frail in 2008 were alive 6 years later vs. 52% of the frail; the hazard ratio (HR) was 3.5, confidence interval (CI) 2.2–5.4.

The total loss to follow-up was 24% (n=14) (13% wrong telephone number, 6% refusal, 2% were in a nursing home, and 3% for other reasons). Those who were lost to follow-up did not differ significantly from the participants (those who died and those who were interviewed) in terms of age, gender, marital status, country of origin, education level, living alone, or baseline VES-13 score. Eighty-five interviews (30%) were conducted with a proxy respondent.

In order to assess frailty transitions we studied the population who were interviewed both in 2008 and again in 2014 (n=281). These participants were divided into four groups:

- Non-frail (n=54) – those participants who were non-frail in 2008 (mean VES 1.1 ± 1.5) and remained non-frail in 2014 (mean VES 1.0 ± 0.7) with the addition of six subjects who went from frail in 2008 to non-frail in 2014 (It was assumed that this transition was due to an acute episode in 2008)
- Transition (n=63) – those who were non-frail in 2008 (mean VES 1.4 ± 0.7) and became frail in 2014 (mean VES 6.0 ± 2.5)
- Frail (n=61) – those who were frail in both 2008 (mean VES 8.0 ± 1.8) and 2014 (mean VES 6.7 ± 2.5) and whose scores either stayed the same or improved (lower VES)
- More frail (n=103) – those who were frail in 2008 (mean VES 6.1 ± 2.0) and 2014 (mean VES 9.0 ± 1.4) and whose score worsened (higher VES).

Analysis of the demographic characteristics in 2014 revealed that the non-frail group was younger, had fewer women, less memory loss and higher functioning than the other groups. Function was most impaired in the more frail group, with a higher percentage of falls, cognitive impairment and needing help at home. The non-frail group had fewer hospitalizations, and fewer reported use of home care and caregivers. The frail and more frail groups had similar percentages of hospitalizations. Sensitivity analysis, in which we removed the six people who moved from frail in 2008 to non-frail in 2014, did not show a difference. The more frail group had higher percentages of ER visits, CGA, and having a formal caregiver [Table 2].

The logistic regression models of health services utilization demonstrated that the transition group, frail group and more frail group were associated with a greater risk of requiring help on a regular basis, having a formal caregiver, and requiring more home care compared to the non-frail group (P < 0.05). The more frail group had the highest risk for requiring help on a regular basis, having a formal caregiver, and visiting the ER (39.667, 31.871, and 2.115, P < 0.05) [Table 3].

### DISCUSSION

Assessing frailty transitions between 2008 and 2014 we found that almost one-fifth of the surviving population stayed non-frail, one-fifth became frail, another one-fifth stayed frail, and more than one-third became more frail. The group that stayed non-frail was younger, more functional and used fewer...
follow-up percentages were similar in both studies. Due to the longer follow-up period, incident frailty and lost to follow-up who died was much higher in the Ottenbacher study, perhaps although the percentage of participants who remained frail or not disabled at baseline. Frailty status was assessed every 18 months using the Fried criteria for 4.5 years in a longitudinal study [14]. They concluded that transitions to states of greater frailty were more common than transitions to states of lesser frailty, and that transition to a state of being non-frail was very unlikely. Their findings were confirmed by Xue and team [15] using data from the Women's Health and Aging Study II. Our findings are consistent with the findings of Gill et al. [14], although we acknowledge the differences in our methodology. Our study included two time points while their study examined multiple assessment points over time.

Our study found that any transition toward frailty was a risk for greater health services utilization. While it has been shown that frailty increases the risk for greater health services utilization, Gill et al. [14] in 2006 examined transitions between frailty states in 754 community-dwelling older people who were not disabled at baseline. Frailty status was assessed every 18 months using the Fried criteria for 4.5 years in a longitudinal study [14]. They concluded that transitions to states of greater frailty were more common than transitions to states of lesser frailty, and that transition to a state of being non-frail was very unlikely. Their findings were confirmed by Xue and team [15] using data from the Women's Health and Aging Study II. Our findings are consistent with the findings of Gill et al. [14], although we acknowledge the differences in our methodology. Our study included two time points while their study examined multiple assessment points over time.

Our study is limited by assessments of frailty at only two points in time. We do not have information on transitions that may have occurred between these time points. In addition, we conducted telephone interviews that may be limited by recall bias and hearing impairment in older people. The strengths of our study are extensive follow-up of health services utilization as well as information on geriatric syndromes and demographics of our participants. In addition, we used the simple and easy to administer VES-13 measure of frailty. Our results were comparable to those of a study that used the performance-based and more complicated to administer, Fried measure of frailty.

Identifying frailty in older people has practical implications for clinical decision making. It has been recommended that the treatment goals for older people with hypertension be determined by their frailty status. A systolic blood pressure of 140–160 is recommended for a frail older person, while a goal of 160–190 is adequate for a very frail older person with a limited life expectancy [22]. In addition, interventions have been developed to prevent and treat frailty. These interventions are often multidisciplinary, with emphasis on an exercise program, nutritional counseling and CGA [23,24]. Some researchers are even calling for widespread screening for frailty in all older people over 70, especially those who have lost weight due to chronic illness [25].

**CONCLUSIONS**
Transitions to states of greater frailty over time are common. Any transition from the non-frail state increases health services utilization. A simple tool, such as the VES-13, could be used to identify early transitions to frailty. Implementing interventions to prevent or delay the transition to frailty should be encouraged.
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Capsule

An oncohistone deranges inhibitory chromatin

Missense mutations (that change one amino acid for another) in histone H3 can produce a so-called oncohistone and are found in a number of pediatric cancers. For example, the lysine-36-to-methionine (K36M) mutation is seen in almost all chondroblastosomas. Lu et al. show that K36M mutant histones are oncogenic, and they inhibit the normal methylation of this same residue in wild-type H3 histones. The mutant histones also interfere with the normal development of bone-related cells and the deposition of inhibitory chromatin marks.

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Capsule

A role for PKCa in Alzheimer’s disease

The neurodegeneration that occurs in Alzheimer’s disease is thought to be due to the accumulation of a protein called amyloid-β (Aβ). Alfonso et al. identified activating mutations in protein kinase Ca (PKCa) in a large cohort of families in which late-onset Alzheimer’s disease was diagnosed. Pharmacologically inhibiting PKCa or deleting the gene encoding it prevented Aβ from impairing synaptic activity in mouse hippocampal tissue slices. Thus, PKCa variants may mediate the pathological effects of Aβ in some patients with late-onset Alzheimer’s disease.

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