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ORIGINAL RESEARCH

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Influenza infection is not associated with phenotypical frailty in older patients, a prospective cohort study

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Abstract

Background and Aims: Influenza is a challenging infectious illness for older adults. It is not completely clear whether influenza is associated with frailty or functional decline. We sought to determine the association between incident influenza infection and frailty and prefrailty in community patients over 50 years of age. We also investigated the association between influenza vaccination and frailty and prefrailty as a secondary aim.

Methods: This was a prospective community cohort study from October 2019 to November 2020 in participants over 50 years. The primary outcome was the development of frailty as defined by three of five frailty criteria (slow gait speed, low grip strength, 5% weight loss, low energy, and low physical functioning). The primary predictor was a positive polymerase chain reaction (PCR) for influenza infection. Influenza vaccination was based on electronic health record reviewing 1 year before enrollment. We reported the relationship between influenza and frailty by calculating odds ratios (OR) with 95% confidence intervals (CI) after adjustment for age, sex, socioeconomic status, Charlson Comorbidity Index (CCI), influenza vaccine, and previous self-rated frailty from multinomial logistic regression model comparing frail and prefrail to nonfrail subjects.

Results: In 1135 participants, the median age was 67 years (interquartile range 60–74), with 41% men. Eighty-one participants had PCR-confirmed influenza (7.1%). Frailty was not associated with influenza, with an OR of 0.50 (95% CI 0.17–1.43) for frail participants compared to nonfrail participants. Influenza vaccination is associated with frailty, with an OR of 1.69 (95% CI 1.09–2.63) for frail compared to nonfrail. Frailty was associated with a higher CCI with an OR of 1.52 (95% CI 1.31–1.76).

Conclusion: We did not find a relationship between influenza infection and frailty. We found higher vaccination rates in participants with frailty compared to nonfrail

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participants While influenza was not associated with frailty, future work may involve longer follow-up.

KEYWORDS
frailty, Influenza, older adults, vaccination

1 | INTRODUCTION

Influenza is an acute respiratory illness that impacts older adults and can cause substantial morbidity and mortality. Clinicians are often concerned that influenza infection will cause frailty with functional decline after infection. Influenza typically occurs in the months of November through April in the Northern Hemisphere.[1] Influenza mortality in the United States ranges from 12,000 to 61,000 individuals.[2] Of equal concern, patients may suffer from debility and disability after an illness such as influenza. Investigators have found an association between frailty and COVID-19.[3] The development of frailty has many established risk factors, including advanced age,[4] female sex,[4,5] educational level,[5] socioeconomic status,[4] and comorbid health conditions.[6] The association of frailty with acute infectious illnesses such as influenza is becoming more important as clinicians are having concerns about long term functional decline with COVID-19.[7] However, questions remain about the association of influenza with frailty.

Anecdotally, clinicians often view frailty and functional decline after influenza as an important clinical concept. Clinicians face inherent challenges in reviewing the current evidence of frailty and influenza. Researchers and clinicians do not utilize one standard definition of frailty despite efforts to do so.[8] The two common methods of defining frailty involve the accumulation of clinical deficits[6] and the phenotype of frailty defined in the Cardiovascular Health Study.[9] Each method has its own strengths and weaknesses.[10] It is not clear which definition of frailty best captures the impact of acute infections such as influenza on frailty outcomes. There may be other measures that better reflect functional outcomes. Loss of muscle mass leading to sarcopenia may be more clinically relevant.[11] Advanced glycation end products may be another biomarker of accelerated aging and a potential measure of functional decline.[12]

Patients with frailty suffer some important clinical consequences, including waning vaccine efficacy with suboptimal antibody titers due to a poor immune response.[13,14] The decrease in efficacy of influenza vaccinations may be a result of immunosenescence.[15] It is unclear how influenza infection, as a common but serious viral infection in older adults, is associated with frailty as defined by the phenotype of frailty, which incorporates both functional measures and self-report. Clinicians and patients recognize that the severity of influenza can vary from medically attended cases to mild cases at home. Lastly, it is important to determine the association of influenza vaccination and frailty in older adults. As our primary aim, we sought to determine the association of incident influenza infection in the community and the phenotype of frailty in a population of ambulatory patients over the age of 50 years. Our secondary aim is to determine the association of influenza vaccination and frailty in a community population over the age of 50 years. This study will provide unique insights into this relationship of frailty and influenza because influenza was detected using polymerase chain reaction (PCR) and frailty was diagnosed by functional measures, including some novel measures.

2 | METHODS

2.1 | Design and setting

This was a prospective cohort study of a community-based cohort. This is a secondary analysis of a previously reported cohort.[16] We are reporting our results using the STROBE guidelines for a cohort study.[17] The study occurred within a primary care setting in Southeastern Minnesota. The study was conducted prospectively in October 2019 with a medical record review from October 2016. We collected data until November 2020. All participants provided written consent for enrollment. The Mayo Clinic Institutional Review Board reviewed and approved the study (IRB number 19-004142). We conducted the study according to the principles of the Declaration of Helsinki.[18]

2.2 | Participants

Participants were over 50 years old and had primary care enrollment at Mayo Clinic, an academic medical center, with at least one visit within 3 years of study enrollment. We excluded participants if they resided outside the catchment area, if they refused electronic health record (EHR) review, or if they received primary care outside of the Mayo Clinic. We excluded participants with cognitive impairment (clinical dementia), immobility (could not ambulate), any acute respiratory infection before enrollment and during influenza season, and those who had previous hospitalization in the 6 months prior. We also excluded participants who resided outside of Minnesota for greater than 2 weeks during the influenza season.

2.3 | Recruitment for cohort

The research team recruited participants using mailed invitations, classified ads, and brochures. In the mailing, participants received an invitation letter and an informational flyer.

2.4 | Study procedures

At the consent (enrollment) visit, participants answered a questionnaire that included self-reported frailty measurements. Participants were instructed on home nasal and throat self-swabbing techniques to be performed when they developed an acute respiratory infection (ARI) with the option to complete a clinic visit where a nurse would complete the swab. We have published the details previously.[16] During the influenza season, October 1, 2019 to April 30, 2020 (influenza season), participants contacted the study team when ARI symptoms occurred. If participants met prespecified criteria (two symptoms from upper, lower, or systemic symptoms), they would complete aswab for influenza. If needed, participants communicated with their primary care medical team for clinical treatment. We invited participants to complete a second study visit between July 2020 and November 2020 for functional frailty measurements and questionnaires. This visit was voluntary as the COVID-19 pandemic influenced research visits. Those who participated in the second visit with complete outcomes were included in the analysis.

2.5 | Outcomes

The primary outcomes were functional frailty measures collected in the summer of 2020 following the 2019–2020 influenza season. We collected frailty measures more than 3 months after the flu season (median: 7 months (interquartile range [IQR] 5–12 months)) following infection, which minimized acute functional decline following influenza infection. Our primary measure of frailty involved the phenotype of frailty described in the Cardiovascular Health Study.[9] We measured (1) grip strength, (2) walking speed, (3) self-reported energy from the short form-36 (SF36), (4) weight loss and (5) self-reported physical activity from the SF36. We defined the frailty criterion for grip strength as a maximum grip of <35.5 kg in men and <20 kg in women.[19] Participants performed a 6-min walk test as the standard for gait speed. We defined the frailty criterion as <1.0 m/s, which corresponds to an accepted diagnosis of sarcopenia.[11] Participants reported weight loss of >5% on the questionnaire.[20] We used two self-reported measures for the frailty criterion using the SF36, physical functioning and energy/fatigue.[21] Participants scoring in the bottom quartile of physical function and/or energy/fatigue were each considered positive criteria for frailty. For the categorization of frailty criteria, patients were considered frail if three or more criteria were met and prefrail if two criteria were met. Patients were without frailty (nonfrail) when they met none or only one criteria. We reported total meters walked in 6 min.

2.6 | Predictors

The primary predictor was influenza infection as diagnosed by PCR (Simplexa Flu A/B and RSV Direct; DiaSorin Molecular). The secondary predictor was influenza vaccination. We abstracted influenza vaccination from the EHR in the 1 year before enrollment.

Additionally, we collected demographic information from either the EHR or self-report. Age, sex, and race/ethnicity (classified as non-Hispanic White and other) were established from the EHR. Patients provided marital status and educational status on the study questionnaire. We categorized educational status as high school graduate or less, some college, 4-year college graduate, graduate or professional school, and other and marital status as married (or in married like relationship) versus all others. We determined if the patient lived in a rural location versus urban location by using the census urban–rural classification.[22] Participants reported working status (full, part-time, and not working). For socioeconomic status, the team calculated the HOUSES index using a previously described methodology. HOUSES calculates socioeconomic status based upon publicly available characteristics within the home.[23] HOUSES is an individual level measure of socioeconomic status that evaluates real property data using the number of bedrooms, number of bathrooms, square footage of the unit, and estimated building value of the property.

For other important predictors, we determined comorbid health conditions that could be associated with influenza. Specifically, we used the patient's history of asthma, chronic obstructive pulmonary disease, congestive heart failure (CHF), diabetes, and any heart or lung condition by looking at the EHR in the 3 years before enrollment. We also reported the Charlson Comorbidity Index (CCI)[24] which measures comorbid health conditions and age using billing diagnosis codes from patient's history using ICD 10. Body mass index (BMI) and smoking status were determined on self-report during the enrollment questionnaire. Participants also completed the FRAIL self-reported questionnaire at enrollment. The FRAIL is a self-report questionnaire to evaluate frailty.[25]

2.7 | Statistical analysis

We collected and presented the descriptive analysis of the study cohort by influenza status. We compared demographic characteristics and the individual frailty criteria in participants with and without influenza by reporting count (percentages) and using χ^2 for categorical variables and by reporting median (IQR) and using the Kruskal–Wallis test for continuous variables. Furthermore, we looked at the association of our frailty outcome with influenza infection using multinominal logistic regression (using nonfrail as our reference). We reported odds ratios (OR) of frailty and prefrail with 95% confidence intervals (CI) in both an unadjusted fashion as well as with multivariable adjustment for age, sex, CCI, HOUSES scores, influenza vaccination, and FRAIL score[25] at enrollment. The adjustment variables were based upon previous clinical work. We considered a two-sided test with a p value less than 0.05 as significant, and all analyses were conducted in SAS statistical software (version 9.4M7).

3 | RESULTS

3.1 | Subject characteristics

In our study, 2326 participants initially consented for the primary study. A total of 1135 participants were analyzed in the present study after returning for follow-up and completing the five elements of our frailty outcome measurement. We found that those who participated were generally younger healthier than those who opted not to participate. (Supporting Information: Table 1) The median age of the cohort at enrollment was 67 years (IQR 60–74), and there were 670 women (59.0%). Regarding living situation, 78.9% were married or in a married like relationship, and 79.5% were living in an urban area. The cohort was largely non-Hispanic white (96.2%), and the majority 58.6% possessed a college bachelor's degree or higher. A total of 352 (31%) had received the influenza vaccination in the year before enrollment. For the primary predictor of influenza, we found that 81 (7.1%) had influenza during the influenza season. (Table 1) We found that 16 of the cases were influenza B and 65 were influenza A.

3.2 | Influenza infection and enrollment characteristics

The participants with influenza were younger at 65 years (IQR 59–70) compared to 67 years (IQR 60–75) in participants without influenza ($p = 0.008$). Participants with influenza were more likely to be working (40.5%) than participants without influenza (27%) ($p = 0.028$). We found that those with influenza had a lower median CCI score than those without influenza ($p = 0.03$). For other potential confounders, we found no difference between those with and without influenza (Table 1).

3.3 | Frailty and association with influenza and influenza vaccination

A total of 151 participants (13.3%) met the criteria for frailty, and 166 (14.6%) were prefrail. We found that participants with influenza walked 513.3 m (SD 76.5) in 6 min compared to 485.9 m (SD 105.6) in participants without influenza ($p = 0.033$) resulting in corresponding to gait speeds of 1.4 m/s (SD 0.2) compared to 1.3 m/s (SD 0.3), respectively. Participants with influenza were less likely to be in the lower quartile for physical function compared to noninfluenza participants ($p = 0.05$). All other frailty criteria were found to be no different by influenza infection status (Table 2).

In general, influenza was not associated with being frail. We found that only 3% of frail subjects ($n = 5$) and 6% of prefrail subjects ($n = 9$) had influenza infection compared to 8% of nonfrail subjects having had an influenza infection. After adjustment for age, HOUSES, self-reported FRAIL score, influenza vaccine status, and Charlson Index, we found the OR of frailty (compared to nonfrail) for those with influenza infection was 0.50, (95% CI 0.17–1.43) compared to participants without influenza. For the OR of influenza infection on prefrail status, we found an adjusted OR of 0.71 (95% CI 0.33–1.56) compared to participants without influenza (Table 3).

For the secondary predictor of influenza vaccination, 69 participants with frailty (43.9%) received the influenza vaccination compared to 229 participants without frailty (27.8%) ($p < 0.001$). In the unadjusted analysis, the relationship between influenza vaccination and frailty compared to nonfrailty was 2.04 (95% CI 1.44–2.89). After adjustment, participants who received the vaccine were more likely to be frail, with an adjusted OR of 1.69 (95% CI 1.09–2.63). There was no association between influenza vaccination and prefrail status versus nonfrail status in adjusted analyses (Table 3).

3.4 | Frailty and other predictors

We have reported frailty and prefrailty by other collected demographic characteristics not used in the analysis including age by decade, marital status, working status, rural location, CHF, asthma, chronic obstructive lung disease, body mass index, and smoking status. (Supporting Information: Table 2) Among measures used in the final adjusted model, we found an association of frailty with the Charlson Index, with an adjusted OR of 1.52 (95% CI of 1.31–1.76). We did not find an association of frailty with the HOUSES index (Table 3).

4 | DISCUSSION

In this study of 1135 patients, we found no association between incident influenza infection based on community surveillance and frailty 3 months after infection. We discovered that influenza was not associated with prefrailty as well. Our study is unique because of three major components. First, influenza infection is based upon community-based surveillance and not upon medically attended infection. Second, the diagnosis of influenza was made by PCR and not self-report. Third, we used the rigorous phenotype of frailty which included functional assessment. Previous studies have given some insight into the relationship between influenza and frailty; however, there are limitations to the diagnosis of influenza and frailty as well as the location of diagnosis. In a previous study of 114 patients using matched controls, the authors collected swabs in the community for general acute respiratory illness (but not specifically PCR diagnosed influenza). The authors found that influenza-like symptoms were not associated with frailty as measured using the Vulnerable Elders Survey 13, which is a self-report measure.[26] In a large Canadian survey study of participants with self-reported influenza or influenza-like illness, 40% indicated a recovery greater than two weeks, and long-term function loss occurred in 3% by self-report.[27] This study was collected from a community cohort.[27] Both studies looked at community surveillance, which is similar to our population; however, they both used self-report for functional outcome and for influenza-life illness. In a recent study of

TABLE 1 Characteristics at enrollment of Patients with and without Influenza during Influenza Season

	Without Influenza (*N* = 1054)	With Influenza (*N* = 81)	Total (*N* = 1135)	*p* value
Age at Enrollment (years)				0.008[a]
Mean (SD)	67.5 (9.3)	64.6 (7.2)	67.3 (9.2)	
Median (IQR)	67 (60–75)	65 (59–70)	67 (60, 74)	
Sex, *n* (%)				0.965[b]
Female	622 (59.0%)	48 (59.3%)	670 (59.0%)	
Male	432 (41.0%)	33 (40.7%)	465 (41.0%)	
Race/ethnicity, *n* (%)				0.574[b]
Non-Hispanic White	1015 (96.3%)	77 (95.1%)	1092 (96.2%)	
Other	39 (3.7%)	4 (4.9%)	43 (3.8%)	
Educational level, *n* (%)				0.121[b]
High school or less	78 (8.6%)	1 (1.4%)	79 (8.0%)	
Some college	295 (32.5%)	23 (31.1%)	318 (32.4%)	
Four-year college graduate	292 (32.2%)	26 (35.1%)	318 (32.4%)	
Graduate or professional school	235 (25.9%)	22 (29.7%)	257 (26.2%)	
Other	8 (0.9%)	2 (2.7%)	10 (1.0%)	
Missing	146	7	153	
Marital status, *n* (%)				0.684[b]
Married/living with someone in a marriage-like relationship	705 (79.0%)	57 (77.0%)	762 (78.9%)	
Other	187 (21.0%)	17 (23.0%)	204 (21.1%)	
Missing	162	7	169	
HOUSES, *n* (%)				0.245[b]
Quartile 1 (lowest SES)	104 (10.5%)	9 (11.4%)	113 (10.6%)	
Quartile 2	252 (25.5%)	13 (16.5%)	265 (24.8%)	
Quartile 3	295 (29.9%)	23 (29.1%)	318 (29.8%)	
Quartile 4 (highest SES)	337 (34.1%)	34 (43.0%)	371 (34.8%)	
Missing	66	2	68	
Rural location, *n* (%)				0.695[b]
Living in rural area	215 (20.4%)	18 (22.2%)	233 (20.5%)	
Living in urban area	839 (79.6%)	63 (77.8%)	902 (79.5%)	
Working status, *n* (%)				0.028[b]
Working full time for pay (35 or more hours a week)	244 (27.0%)	30 (40.5%)	274 (28.0%)	
Working part-time for pay	150 (16.6%)	7 (9.5%)	157 (16.1%)	
Not working for pay at present	510 (56.4%)	37 (50.0%)	547 (55.9%)	
Missing	150	7	157	
Influenza Vaccination, *n* (%)	326 (30.9%)	26 (32.1%)	352 (31.0%)	0.827[b]
Charlson Index				0.031[a]
Median (IQR)	1 (0–2)	0 (0–1)	1 (0–1)	

(Continues)

TABLE 1 (Continued)

	Without Influenza (*N* = 1054)	With Influenza (*N* = 81)	Total (*N* = 1135)	*p* value
Congestive heart failure, *n* (%)	40 (3.8%)	1 (1.2%)	41 (3.6%)	0.234[b]
Asthma, *n* (%)	98 (9.3%)	11 (13.6%)	109 (9.6%)	0.207[b]
Chronic obstructive lung disease, *n* (%)	63 (6.0%)	5 (6.2%)	68 (6.0%)	0.943[b]
Any heart or lung disease, *n* (%)	608 (57.7%)	48 (59.3%)	656 (57.8%)	0.782[b]
Diabetes, *n* (%)	134 (12.7%)	7 (8.6%)	141 (12.4%)	0.284[b]
Body mass index (kg/m^2)				0.174[a]
Mean (SD)	28.1 (5.7)	29.0 (5.7)	28.2 (5.7)	
Median (IQR)	27.1 (24.0–31.2)	28.1 (24.7–32.9)	27.2 (24.0–31.3)	
Missing	153	7	160	
Smoking status, *n* (%)				0.524[b]
Never	691 (67.6%)	50 (64.1%)	741 (67.4%)	
Ever	331 (32.4%)	28 (35.9%)	359 (32.6%)	
Missing	32	3	35	
Self-reported FRAIL score, *n* (%)				0.635[b]
Nonfrail	837 (80.3%)	65 (80.2%)	902 (80.3%)	
Prefrail	194 (18.6%)	16 (19.8%)	210 (18.7%)	
Frail	11 (1.1%)	0 (0.0%)	11 (1.0%)	
Missing	12	0	12	

Note: FRAIL scale was categorized as follows: nonfrail (0 point); prefrail (1–2 points), and frail (3–5 points).

Abbreviations: IQR, Interquartile Range (Quartile 1, Quartile 3); SD, standard deviation; HOUSES Index, socioeconomic indicator using housing characteristics;[23] FRAIL, Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight.[25]

[a]Kruskal–Wallis *p* value.

[b]χ^2 *p* value.

hospitalized patients with laboratory confirmed influenza, 346 patients with influenza were phoned for self-reported functional assessment 30 days following dismissal. The authors found 8.4% mortality, 8.2% moderate decline and 9.9% catastrophic decline. This study used self-report and was based on hospitalized patients.[28] Our study is uniquely rigorous because we specifically identified influenza using PCR to avoid other less virulent viral infections. We used the phenotype of frailty with both self-report and objective data of gait speed and grip strength, which assists with the objective physical changes of frailty. Our findings are important, as they more accurately describe the relationship between physiological decline and viral infection in the community compared to previous studies.

In addressing the question of whether the influenza vaccine can be a protective factor for frailty by reducing the risk of influenza versus a surrogate marker for high-risk conditions, we found that participants with frailty had a 46% influenza vaccination rate compared to 28% without frailty; thus, there was a higher vaccination rate in participants with frailty. These results may suggest that influenza vaccination might function as a surrogate marker for high-risk conditions instead of influenza vaccine resulting in frailty (i.e., confounder), as there is no biological reason to believe influenza vaccine causes frailty. In support of this interpretation, we assessed the association between the CCI and frailty, and the results suggested that the CCI was associated with frailty. Thus, our study results support that patients should receive an influenza vaccination.[29] We are encouraged that more patients who were frail received the vaccination, which reinforces our hopes that the highest-risk patients receive the vaccination. However, aging per se and perhaps frailty as an indicator of accelerated aging reduces the effectiveness of influenza vaccination,[13] most likely due to immunosenescence.[30]

We found that the strongest predictor of future frailty was a higher score on the CCI, which indicates a higher burden of chronic illnesses. This could be expected, as frailty is often defined by the accumulation of either illnesses or symptoms.[31] We did not find a relationship between self-reported FRAIL scores and phenotypical frailty, which was likely secondary to the low number of patients with frail status by self-report and by exclusion criteria. The evidence of self-reported physical limitations and further functional decline was evaluated in 998 patients in St. Louis who self-reported physical

TABLE 2 Frailty Characteristics at follow up visit in patients with and without influenza during influenza season

	Without influenza (*N* = 1054)	With influenza (*N* = 81)	Total (*N* = 1135)	*p* value
Frail Score, *n* (%)				**0.070**
NonFrail	757 (71.8%)	67 (82.7%)	824 (72.6%)	
Prefrail	145 (13.8%)	9 (11.1%)	154 (13.6%)	
Frail	152 (14.4%)	5 (6.2%)	157 (13.8%)	
Six minute total distance (m)				**0.033**
Mean (SD)	485.9 (105.6)	513.3 (76.5)	487.9 (104.0)	
Median (IQR)	495 (420–560)	515 (475–570)	498 (425–560)	
Six minute gait speed (m/s)				**0.033**
Mean (SD)	1.3 (0.3)	1.4 (0.2)	1.4 (0.3)	
Median (IQR)	1.38 (1.17–1.56)	1.43 (1.32–1.58)	1.38 (1.18–1.56)	
Six minute gait speed < 1.0 m/s, *n* (%)				**0.064**
No	931 (88.3%)	77 (95.1%)	1008 (88.8%)	
Yes	123 (11.7%)	4 (4.9%)	127 (11.2%)	
Grip strength max (kg)				**0.212**
Mean (SD)	31.6 (10.9)	33.6 (11.7)	31.7 (11.0)	
Median (IQR)	29.5 (24.0–37.9)	30.5 (24.1–42.9)	29.5 (24.0–38.2)	
Grip strength max < 35.5 kg men and < 20 kg women, *n* (%)				**0.111**
No	803 (76.2%)	68 (84.0%)	871 (76.7%)	
Yes	251 (23.8%)	13 (16.0%)	264 (23.3%)	
Weight loss > **5%**, *n* (%)				**0.399**
No	945 (89.7%)	75 (92.6%)	1020 (89.9%)	
Yes	109 (10.3%)	6 (7.4%)	115 (10.1%)	
SF-36 physical functioning scale				**0.084**
Mean (SD)	82.5 (20.9)	88.2 (12.9)	82.9 (20.5)	
Median (IQR)	90 (75–95)	90 (80–100)	90 (75–95)	
SF-36 physical functioning scale 1st quartile, *n* (%)				**0.049**
No	766 (72.7%)	67 (82.7%)	833 (73.4%)	
Yes	288 (27.3%)	14 (17.3%)	302 (26.6%)	
SF-36 energy/fatigue scale				**0.051**
Mean (SD)	65.6 (18.1)	69.0 (18.9)	65.9 (18.1)	
Median (IQR)	70 (55–80)	75 (60–85)	70 (55–80)	
SF-36 energy/fatigue scale 1st quartile, *n* (%)				**0.196**
No	721 (68.4%)	61 (75.3%)	782 (68.9%)	
Yes	333 (31.6%)	20 (24.7%)	353 (31.1%)	

Note: Bold values are statistically significant $p < 0.05$.

Abbreviations: IQR, interquartile range (Quartile 1, Quartile 3); SD, standard deviation; SF, short form.

TABLE 3 Unadjusted and adjusted odds ratios for risks of frailty

	Univariate association			Multivariable association		
		95% confidence interval			95% confidence interval	
	Odds ratio	Lower limit	Upper limit	Odds ratio	Lower limit	Upper limit
Age (1 Year)						
Nonfrail	1.00	Reference		1.00	Reference	
Prefrail	1.05	1.03	1.07	1.05	1.02	1.07
Frail	1.12	1.09	1.14	1.10	1.07	1.13
Influenza vaccine (yes vs. no)						
Nonfrail	1.00	Reference		1.00	Reference	
Prefrail	1.40	0.97	2.02	1.30	0.87	1.92
Frail	2.04	1.44	2.89	1.69	1.09	2.63
Influenza infection (yes vs. no)						
Nonfrail	1.00	Reference		1.00	Reference	
Prefrail	0.70	0.34	1.44	0.71	0.33	1.56
Frail	0.37	0.15	0.94	0.50	0.17	1.43
Charlson index (1 comorbidity)						
Nonfrail	1.00	Reference	1.00	Reference		
Prefrail	1.49	1.31	1.70	1.25	1.08	1.46
Frail	1.94	1.71	2.19	1.52	1.31	1.76
HOUSES (Q2 vs. Q1)						
Non-Frail	1.00	Reference	1.00	Reference		
Prefrail	0.58	0.31	1.08	0.59	0.31	1.14
Frail	0.53	0.30	0.95	0.68	0.33	1.40
HOUSES (Q3 vs. Q1)						
Nonfrail	1.00	Reference		1.00	Reference	
Prefrail	0.57	0.31	1.05	0.66	0.35	1.24
Frail	0.57	0.32	0.98	0.92	0.46	1.86
HOUSES (Q4 vs. Q1)						
Nonfrail	1.00	Reference		1.00	Reference	
Prefrail	0.53	0.30	0.96	0.74	0.40	1.38
Frail	0.30	0.17	0.53	0.68	0.32	1.41
Self-reported FRAIL score (prefrail/ frail vs. nonfrail)						
Nonfrail	1.00	Reference		1.00	Reference	
Prefrail	3.51	2.33	5.28	2.92	1.84	4.63
Frail	10.17	6.91	14.95	9.92	6.23	15.80

Note: FRAIL scale was categorized as follows: nonfrail (0 point); prefrail (1–2 points), and frail (3–5 points). Odds ratios were generated from a multinominal logistic regression model with follow up frail score (frail, prefrail, and nonfrail) as defined by the CHD as the outcome using nonfrail as the reference category. Predictors were evaluated at enrollment (July 2019 to November 2019) except for Influenza infection which was determined during influenza season (October 2019 to April 2020). Multivariable multinominal logistic includes all covariates reported including age (years), HOUSES (Q1, Q2, Q3, Q4), FRAIL Score (frail, prefrail, and nonfrail), Charlson index (number of comorbidities), influenza vaccine (yes and no) and in and Influenza infection.

Abbreviations: FRAIL, Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight;[25] HOUSES, socioeconomic index based upon housing characteristics;[23] Q, Quartile.

limitations associated with functional declines in the subsequent 2 years.[32] This study found that self-report better predicted further functional decline compared to objective balance and strength findings, including gait speed.[32] Socioeconomic status as measured by HOUSES did not predict frailty. It was reported in quartiles, with the lowest quartile having a higher risk of hospitalization and comorbid health.[33]

Our study has many strengths and some limitations. The study used a well-validated method of collecting comprehensive frailty characteristics, which aided in understanding the physical functioning changes after influenza infection. The study was based on community-based surveillance, which better captured influenza cases in the community not relying on medical visits such as hospitalization or health care access. There is major scientific merit in addressing the study question as medically attended influenza might be subject to detection bias distorting or obscuring the relationship between influenza and frailty. The diagnosis of influenza was also well validated with prospective swabs concurrent with respiratory symptoms. Our study setting using a community-based approach allowed us the option to see the full spectrum of influenza. The limitations include the potential for missing influenza if patients did not receive a nasal swab despite our best effort via community-based surveillance. This was minimized as the study team lowered barriers to testing by using self-swabs and not requiring a medical visit. As this was an observational study, there could be other factors that account for the development of frailty that were not described. Our study population was younger and had no mobility issues at enrollment. We did not collect new comorbid health concerns between enrollment and primary assessment. We used self-report information on influenza vaccinations. Our study setting generalizes to the upper midwest of the United States and may not generalize to other parts of the country or world.[34] The number of patients with influenza may have been influenced by COVID-19 as patients changed behaviors during the season, and universal masking was implemented in March 2020 in Minnesota. There was a small overlap between public health measures in March 2020 and the completion of the study in April 2020. It is possible that COVID infection could impact our study as clinical and research testing was not widely available from January 2020 to May 2020. We used the commonly described and accounted for risk factors for frailty, including age, sex, socioeconomic issues, comorbid health conditions, and BMI.

In this study of 1135 participants based on community-based surveillance, we found that there was no difference between developing influenza and frailty. We are encouraged by these findings, as we did not see long-term sequelae of influenza on frailty in this community population. We did find a relationship between frailty and obtaining the influenza vaccination, which indicates that participants with a higher comorbidity burden elected to receive their influenza vaccination. As our study was community-based surveillance and included both mild and severe influenza cases, future studies need to assess the role of the severity of influenza in frailty. We recognize that further evaluation in a longitudinal fashion could help determine a different trajectory for participants.

AUTHOR CONTRIBUTIONS

Paul Takahashi: Conceptualization; investigation; methodology; supervision; writing—original draft; writing—review and editing. **Chung-Il Wi**: Conceptualization; data curation; investigation; methodology; supervision; validation; writing—review and editing. **Euijung Ryu**: Data curation; formal analysis; methodology; supervision; visualization; writing—review and editing. **Katherine King**: Conceptualization; data curation; formal analysis; software; validation; writing—review and editing. **Joel Hickman**: Data curation; formal analysis; writing—review and editing. **Robert Pignolo**: Conceptualization; funding acquisition; investigation; methodology; resources; writing—review and editing. **Young Juhn**: Conceptualization; funding acquisition; investigation; methodology; project administration; resources; supervision; visualization; writing—review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead author (manuscript guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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