Proposal for

Using Machine Learning to Predict Physical Resilience

By

Nathan K Smith

CSCI6903

Dr. Finlay Maguire

June 20th, 2022.

Contents

Abstract

This project aims to understand why individuals with similar health status have different health outcomes. To meet this aim, this project advances our understanding of the physiologic processes underlying risk in aging populations. Risk is defined as the probability of an adverse event occurring within a specified time period (e.g., risk of death in five years) and is an important concept in medicine as estimates of risk influence decisions pertaining to treatment and prognosis. Two concepts represent a range of physiologic processes that contribute to an individual's risk: frailty and physical resilience. Frailty is a well-studied concept frequently used in aging research and geriatric medicine and is broadly defined as a physiologic state of increased vulnerability to health stressors. The related concept of physical resilience, defined as the ability to resist or recover from functional decline following a health stressor, is relatively new in the field of aging and has potential to complement and expand the concept of frailty. However, progress in this area has been limited due to the methodological difficulties inherent in measuring physical resilience. The proposed study will use a machine learning approach to enable prediction and imputation of physical resilience in the Health and Retirement Survey (HRS), a large population-based dataset. By providing a novel approach to conduct a joint large-scale investigation of physical resilience and frailty, this study has significant potential to inform the conceptual discourse, add to the methodological toolset, and build the empirical literature of physical resilience and frailty.

Lay Summary

As our aging population is confronted with new health challenges such as the COVID-19 pandemic, there is a need to improve our understanding of health risks at advanced ages. Risk is an important concept in medicine, as estimates of risk influence decisions pertaining to treatment and prognosis. Two concepts in geriatric medicine are key to our understanding of risk: frailty and physical resilience. Frailty is a well-studied concept frequently used in aging research and geriatric medicine and is broadly defined as a state of increased vulnerability to stressors (for example, a fall). The related concept of physical resilience, defined as the ability to resist or recover from functional decline following a stressor, is relatively new in the field of aging and has potential to complement and expand the concept of frailty. However, research in this area has been limited due to difficulty in measuring physical resilience. The proposed research will use artificial intelligence to predict physical resilience in a large national dataset. By enabling broad estimation of physical resilience, this study will be the first to offer a large, population-based examination of frailty and physical resilience to study what determines risk in older adults.

Introduction

As of July 1st, 2021, approximately 18.5% of the Canadian population was aged 65 or older, and this proportion continues to grow (1). Today, aging individuals are living longer than previous generations. As a result, an increasing number of individuals are reaching advanced ages (80+), promoting unique healthcare needs and considerations. Heightened non-specific vulnerability at these advanced ages is resulting in an increasing number of people who seemingly die from “old age”: treating individual diseases is no longer sufficient to address the needs of this population. As the limits of human longevity continue to be tested, we approach the brink of what is likely to be the next epidemiological transition: from chronic disease to frailty. Broadly considered as an aging-related state of increased vulnerability to health stressors, frailty has emerged as a key concept in understanding the health of older adults. In the literature, the term vulnerability is used in a general sense without an exact definition but can be interpreted as risk of a negative outcome (e.g., hospitalization, death, etc.) after encountering a stressor (e.g., fall, infection, minor surgery, etc.). Thus, a frail individual is an individual who is likely to end up being hospitalized or dying after a seemingly banal event that would not have triggered anything serious in a non-frail (or less frail) individual. Without intervention, the typical progression a frail individual will experience is functional decline, disability, loss of independence, and eventually death. Morley et al. (2006) describe this as the frailty cascade (2). With our population living longer, more adults than ever experience and succumb to frailty. The increasing longevity of populations in Canada and elsewhere globally is changing the needs of its healthcare system and addressing the complex health needs of this population has become a priority. Better understanding frailty is key to adequately address the needs of our growing aging population.

An important consideration is that some individuals, despite having the same level of frailty as measured by conventional methods, maybe be able to better respond to stressors than others, leading to unexplained heterogeneity in outcomes. Frailty measures typically demonstrate inadequate predictive accuracy, with the FI consistently showing the best predictive power for multiple adverse outcomes of all frailty measures. Area under the curve (AUC) is a measure of discrimination, or the ability of the tool (in this case, the frailty measure) to differentiate between those with and without the outcome of interest (in this case, incident hospitalization or death). The AUC values for the FI are typically in the poor to fair range (>0.6 <0.8) depending on the outcome, length of follow-up, and population (3–6). While knowledge of frailty helps improve our ability to predict adverse events, significant unexplained heterogeneity in outcomes remains. This need for a deeper understanding of risk has been highlighted by other authors. As a recent example, Andrew et al. (7) note that heterogeneous outcomes in COVID-19 severity among individuals of similar levels of frailty calls for further consideration of the processes underlying vulnerability.

An interesting feature in the frailty cascade is the potential to recover rather than progress farther down the cascade. Being able to identify who is most likely to recover would improve estimation of risk associated with frailty, and thus would help reduce this unexplained heterogeneity in outcomes. The concept of resilience, broadly defined as the ability to resist or recover from stress, has a long history in of application in various field such a psychology and engineering but has only recently been applied to physical health and aging. More specifically, a new construct termed *physical resilience* has been proposed as a whole-person level characteristic which determines an individual’s ability to resist or recover from functional decline following a stressor (8). Physiologic resiliencies have also been proposed, which determine the physiologic response to a stressor (at the cellular, organ, or organ-system level), and can influence whole-person resilience (i.e., physical resilience) (9). The concept of physical resilience has significant potential to complement and expand upon what frailty offers, and has been proposed to assist in clinical decision making, developing care models, identifying preventative strategies (10), and to aid in the assessment and treatment of frail older adults (11). Recently, there has been an increasing interest in how the concepts of physical resilience and frailty fit together (12–15). Despite the numerous opinion and conceptual articles, no study to date has provided an in-depth empirical evaluation of the two concepts. Determining the patterns and distributions of co-occurrence, and their association with mortality (i.e., do they independently predict mortality, and is resilience an effect modifier of frailty?) would help support and/or inform the current conceptual work, as well as potentially improve estimates of risk in aging populations. However, empirical work in this area has been limited by the methodological difficulties in measuring physical resilience as there is currently no established gold standard.

Literature Review

A review of the relevant literature yielded 21 publications which employed an empirical measure of physical resilience (Table S1), as well as a protocol for a prospective cohort validation study (16). Measures of physical resilience fall into two broad categories: direct and indirect.

Direct Measures of Physical Resilience

Direct measures include those that directly observe maintenance (of functional/health state) or recovery after experiencing a stressor. Direct measures of physical resilience are typically defined in terms of a system, stressor, and state/outcome (10). For example, a measure of physical resilience could be defined as whole-person (system) resilience to hip fracture (stressor) in terms of difficulty completing activities of daily living (ADLs) (state/outcome). These approaches require longitudinal data and the explicit measurement of a stressor.

Many variations in direct measurement exist. For example, Presley et al. 2022 (17) defined resilience as maintenance or improvement in disability scores in a sample of patients undergoing lung cancer treatment over a period of 8 months. Individuals were assigned to a binary classifier of resilient or non-resilient. Compared to the other direct measures described below, this is a very coarse definition, which may have limited use compared to one with more categories. In contrast to this, Pedone et al. 2020 (18) used the change in physical function after a nonspecific “major health event” to determine resilience status. The authors categorized individuals as resilient (maintained function after event), non-resilient (declined before the event), decliners (declined in absence of stressor), and controls (no stressor, no decline). The authors found that resilient individuals were similar to controls in terms of change in activities of daily living (ADLs) and mortality over time. This is an interesting way to broaden the use of a direct physical resilience measure, and to categorize and compare individuals who did not experience a health event. However, it does not allow for consideration of recovery. In addition to this, there was no fine timing of the stressor (all we know is it happened between baseline and 3 years).

Another approach taken by Calle et al. 2018 (19) is to use absolute and relative functional gain after orthopedic surgery and stroke. Absolute functional gain was defined as the difference between the Barthel Index score at discharge and admission, while relative functional gain was defined as the percentage of lost function recovered. The authors examined between recovery and relationship with frailty-related factors (e.g., delirium, ability to walk, sarcopenia), but no overall frailty measure was used. It should be noted that the authors did not actually use the term physical resilience (or even resilience).

Duan-porter et al. 2016 (20) examined resistance and resilience in a cohort of older cancer survivors. The authors defined resistance as a lack of any decline, decline as a drop of 13 or more points of the SF36 physical function subscale, and resilience as regaining at least 50% of lost function. The authors found that the majority of older cancer survivors exhibit resilience. However, this sample is inherently subject to survivor bias.

Colón-Emeric et al. 2019 (21) used latent growth mixture models for 10 functional outcomes in patients with hip fracture to determine common recovery patterns. Individuals were categorize as high, medium and low resilience, and the authors notes that the outcomes had similar slopes within resilience groups.

Colón-Emeric et al. 2020 (22) expands upon the 2019 work by describing approaches to quantify the recovery phenotype and the expected recovery differential (ERD). The recovery phenotype is described as an approach to quantify how quickly and completely an individual recovers using statistical methods. The authors use the previous latent class analysis approach as one method to determine the recovery phenotype, and further describe an approach to use principal component analysis (PCA) in the case of using multiple clinical classification variables that can't be captured as a time series. In their example of pneumonia, the outcomes used to determine the recovery phenotype included length of hospital stay, intensive care unit (ICU) admission, death within 28 days, and discharge location. Their alternative approach, the expected recovery differential, is defined as the expected vs observed recovery based on a population-derived model. In their empirical demonstration, the recovery phenotype typically identified the healthiest individuals as the most resilient, and the least healthy as least resilient. However, the expected recovery differential identified healthy individuals who had worse recovery than expected, and unhealthy individuals who had better recovery than expected. Given these results, the authors suggest the recovery phenotype is useful for characterizing complex recovery patterns, while the expected recovery differential is useful for exploring the biological mechanisms underlying physical resilience.

In addition to describing these two methods, Colón-Emeric et al. provide results that support the idea of an underlying, whole person resilience that cuts across multiple domains (22). This conception of physical resilience is a particularly compelling one: if a latent construct that determines recovery across multiple domains exists (i.e., physical resilience), and could be accurately measured, then studying this construct would offer insights into the types of interventions needed to enhance recovery to several stressors, as well as identification of those at highest risk who would benefit most from such interventions. The authors compared the expected recovery differential of 10 outcomes, created a composite measure of all 10 indicating an individual's total expected recovery differential, then plotted the expected recovery differential of two domains by total ERD quartile grouping. The authors suggest that the grouping of the total ERD supports the existence of a latent, whole-person resilience associated with functional recovery in multiple domains. However, they do note that grip strength ERD and lower extremity ADL ERD are not correlated. As will be discussed below, the importance of outcome choice in studying resilience has been illustrated by Rector et al., when trying to investigate the use of dynamical indicators of resilience (23). Findings such as these underscore the importance of thoughtful variable selection with careful consideration of the variable/system's role in maintaining health.

And lastly, Parker et al. (24) followed up the work of Colón-Emeric et al. with a biomarker study of the expected recovery differential. The authors built a biomarker LASSO regression model that explained 27% of the variance in the expected recovery differential. Taken together, Colón-Emeric et al. provide the most robust and promising measures of resilience with the recovery phenotype and the expected recovery differential (22). These approaches use multiple outcomes to ascertain an overall level of resilience and offer two approaches tailored for different applications. However, the limitation to these, and all direct approaches is that they can only be applied to a small subset of a population who have experienced a specific health stressor. The use of a self-reported "major health event" by Pedone et al. (18) attempts to broaden this limitation, but this approach comes with its own limitations such as the self-reported nature of such events, and this still limits application to those who have experienced some event. In addition to this, there is very limited consideration of frail in these empirical applications of direct measurement.

Indirect Measures of Resilience

Indirect methods include those that do not directly measure recovery, but rather use some sort of proxy measure that is associated (or assumed to be associated) with recovery. The first category of indirect measures are questionnaires. Resnick et al. 2011 (25) evaluate the reliability and validity of the Physical Resilience Measure questionnaire. This paper provided conducted a psychometric evaluation only, with comparisons to general resilience questionnaires (e.g., those used in psychology literature). The performance was not tested against other measures of physical resilience or recovery. The authors conclude that the instrument should be revised prior to further use (25). Park et al. 2022 (26) use this questionnaire to determine whether the effects of frailty and osteoarthritic symptoms are moderated by physical resilience. Using the Tilburg frailty indicator, they find that physical resilience is an effect modifier for both. This is an important finding if the Physical Resilience Measure questionnaire is in fact accurately measuring physical resilience. However, given the limited evidence of this, and the fact that the questionnaire was not validated in the language or study population in which it was used (Korea), this study has a high risk of bias. The question Park et al. have tried to answer is an excellent one with significant implications (i.e., how do frailty and physical resilience relate?), but this needs to be accomplished with more robust methods.

A newer questionnaire, the Physical Resilience Instrument for Older Adults (PRIFOR) was recently evaluated by Hu et al. 2021 (27). The authors examined the predictive validity of PRIFOR using the EQ5D, the Clinical Frailty Scale, and the Katz ADL measures. The authors found that PRIFOR was only associated with the Clinical Frailty Scale at one month after discharge, and suggest it could be used to predict recovery from frailty. Hu et al. 2022 (28) followed up with a psychometric evaluation of the PRIFOR. While the initial investigations of PRIFOR may be promising, this instrument should be further tested with different outcome measures and domains, lengths of follow-up, stressors, as well as a comparison with direct methods of physical resilience measurement to determine its full capability and potential.

The next category of indirect measures is Dynamical Indicators of Resilience (DIORs). DIORs involve assessing variability in the natural stochastic perturbations of a system. DIORs typically reflect a small-scale approach in which stochastic deviations and subsequent return to baseline are considered microrecoveries, and this information is extrapolated to indicate resilience at the system or whole person level. The two most prominent DIORs are variance and cross-correlation of time series measurements, with increasing values indicating diminished resilience. An increase in variance of the specified outcome measure suggests loss of dynamic regulation ability, and an increase in cross-correlation among multiple measures suggests less independence among interconnected systems/subsystems (e.g., measures of cardiac and renal function showing similar fluctuations), and thus diminished resilience. DIORs typically involve many repeated measurements of a specific parameter within a short period. Gijzel et al. 2017 (29) measure self-rated physical, mental, and social health over the course of 100 days in a small sample of 22 institutionalized older adults. They evaluated variance, temporal autocorrelation, and cross-correlation as DIORs, and found that cross-correlation and variance of all three domains was associated with frailty (as measured by the Frailty Index). This study used a small sample size in a non-generalizable population, but the authors demonstrate promising preliminary results for these measures as DIORs.

Continuing from the previous work, Gijzel et al. 2019 (30) examined a time series of postural balance over 30 seconds in a sample of high functioning older adults. The authors found that lower variance and temporal autocorrelation of mediolateral displacement, but not anterioposterior displacement, was associated with higher physical activity (as measured by hikers vs non-hikers). They support this result with reference to studies suggesting that aging-related postural instability starts in the mediolateral direction, making it a more sensitive measure. Additionally, variance was independently associated with a successful aging index at one year post measurement.

In the most recent paper by this group, Gijzel et al. 2020 (31) measured heart rate, physical activity, life satisfaction, anxiety and discomfort in geriatric in-patients with acute illness. Variation in life satisfaction and anxiety independently predicted three-month recovery (increased AUC from 0.70 to 0.79). This study provides initial evidence that the microrecovery approach to resilience can provide modest improvements in recovery prediction at three months when used in conjunction with frailty. Interestingly, only variation in psychological variables was associated with recovery. Similarly, a study by Kolk et al. 2021 (32) found that higher variability in fear of falling was associated with both more decline, and more recovery in a study acutely hospitalized older adults. Variation in step count, pain, and fatigue were not associated. These studies show that while some variables demonstrate the expected association, not all measures are equal.

This point is further illustrated in a study by Rector et al. 2021 (23). The authors demonstrate that using heart rate as a DIOR did not behave as expected in a sample of geriatric inpatients (i.e., higher variance was associated with better ADL function and frailty scores rather than worse, as hypothesized). Physical activity was likely a poor choice as any activity in a clinical setting is likely a good sign. This makes intuitive sense as a stable low activity individual would likely be in worse shape than a variable medium-high activity individual. The authors stress the importance of evaluating variable assumptions in relation to the resilience paradigm. Though not included in this review as the authors were not explicitly examining DIORs, studies by Zhu et al. (33) and Rouche et al. (34) found that blood pressure variability was independently associated with frailty, potentially providing a rationale for the investigation of blood pressure variability as a DIOR.

Taken together, DIORs offer a measure that could be universally applied regardless of disease state or whether an individual has already experienced a specific health event. However, more work is needed to characterize appropriate variables and their relationship with different outcomes.

The next category of indirect measures is discordance with frailty. Wu et al. 2019 (35) propose that the mismatch between disease burden and frailty (based on the residual of a population-derived model) can be used to measure physical resilience. Their method classified individuals into adapters, expected agers, and premature frailers. In a study population of (initially) well-functioning older adult, the authors examined years of able life, years of healthy life, years of healthy and able life, disability, hospitalization, and survival as validation outcomes. All validation outcomes followed the expected gradient, with adapters having the best outcomes, and premature frailers having the worst.

A similar approach was followed by Sotos-Prieto et al. (2021) (36), where physical resilience was defined as accumulating fewer deficits than expected (0.74 per year was expected in their cohort, cited from previous research). An important note is that this analysis only included individuals with a deficit accumulation index above the cohort median. The results indicated that this measure of physical resilience was associated with adherence to the Mediterranean diet. Despite the naming convention the authors chose, this study is essentially using a Frailty Index, and cites early Frailty index work when discussing deficit accumulation. Additionally, there is a field of research that revolves around the pace of aging, in which biological age is estimated and compared to chronological age (37,38). In this way, an individual can be said to age faster or slower than expected. Interestingly, the Frailty Index has been used as a measure of biological age (39). Thus, there is significant, unaddressed, and unexplored conceptual overlap with this area of research.

As one final noteworthy mention in our review, onset of “unhealthy life” (defined as the first occurrence of a major complex disease) has been used as a proxy for robustness (i.e., resistance to decline), and survival following onset has been used as a proxy for resilience (40,41). Taken together, indirect measures offer a way to measure physical resilience without the need of a specific stressor, or longitudinal data. This makes them more broadly applicable than direct measures, however, the proposed indirect measures are not yet firmly established, lacking complete validation (and comparison with direct measures), and some are potentially conceptually problematic given the unexplored overlap with other areas of research.

Summary of Gaps in the Empirical Literature

In summary, there is limited empirical research deploying measures of physical resilience. The majority of studies have been published in the past 5 years, with many proposed approaches and no gold standard method. Direct measures of physical resilience are a more promising avenue as they directly quantify recovery, while indirect measures require more research and thorough validation. Due to these methodological difficulties, population-level descriptive studies have not yet been conducted, and the predictive power and relationship with frailty have not yet been adequately characterized. The recovery phenotype and the expected recovery differential are the most promising of the proposed methods. While Colón-Emeric et al. provide initial support for the idea of a non-specific, whole-person level of physical resilience that is associated with functional recovery in multiple domains, more research is required to confirm this initial observation and to further describe how this underlying construct is related to other relevant clinical characteristics. In particular, how this is related to frailty. The expected recovery differential is particularly well suited to evaluate the relationship between physical resilience and frailty.

Primary and Secondary Research Questions

This work aims to expand upon the work of Colón-Emeric et al. by providing further support for the existence of a non-specific, whole person resilience that cuts across domains, to provide the first population-level descriptive analysis of resilience, and to provide the first in depth analysis of the relationship between frailty and resilience.

Primary Research Question: Can a machine learning approach accurately predict a non-specific, whole person construct of resilience in longitudinal population-based data?

If the primary research question can be adequately achieved, the following questions will be explored:

Secondary Questions: 1) What are the patterns and distribution of resilience? (Specifically, how does it relate to frailty?). 2) Does resilience predict mortality (after accounting for frailty)? Does physical resilience modify the effect of frailty on mortality risk?

Methodology

Data

This study will employ a longitudinal cohort study design, using data from the Health and Retirement Survey (HRS). HRS is well suited for the proposed study as it is one of the largest and longest running active health and aging population-based surveys in the world, offering a nationally representative sample of more than 42,000 individuals over the age of 50 in the United States. HRS has collected information on participants every two years since the first wave in 1992, and includes a detailed exit survey and follow-up protocol which provides near-complete mortality capture, which has been validated using records from the National Death Index (42). Full details on the HRS sample design have been described elsewhere (43). This project will use data solely from the public release files, which can be obtained by creating a free account on the HRS website. Waves 1-14 will be used (1992 – 2018), as this is the latest full data release that includes mortality capture.

Variables

Frailty: A Frailty Index (FI) (44) will be constructed for each individual in each wave. The Frailty Index, based on the cumulative deficit model, is defined as the proportion of deficits an individual has accumulated, out of a minimum of 30 (non-specific, interchangeable) variables from several domains including self-assessed health status, cognition, chronic conditions, function, and physical performance measures. The frailty index ranges from 0 (indicating no deficits) to 1 (indicating all deficits), but it has been consistently observed that the empirical upper limit is approximately 0.70 (45). The frailty index is not a standard set of items, but rather can be constructed from a wide range of health and aging-related variables, making it widely applicable to numerous data sources. The variables (deficits) chosen should cover a wide range of bodily systems, be related to health, and increase in prevalence with age (but cannot saturate too early) (44).

Physical Resilience: An expected recovery differential (22) will be calculated for every instance of a heart attack or stroke from waves 2-13. This will allow for the observation of baseline level of function in the wave prior to the event, as well as the amount recovered at the next wave. This will also allow for an individual's expected recovery differential to change over time if they experience more than one event. Heart attack and stroke were chosen as the stressors because they are relatively common, well characterized major health events that impact multiple functional domains. Additionally, participants are asked about the exact timing of these events in HRS (month and year), which is necessary to get an accurate indication of recovery time. The recovery outcome will be a composite functional difficulty index, defined as the proportion of functional and mobility difficulties, from 0-1. The total items in the index will include difficulty with activities of daily living (walking, bathing, dressing, eating, getting in/out bed, using the toilet), difficulty with instrumental activities of daily living (using the phone, managing money, shopping for groceries, taking medications, preparing hot meals), and mobility difficulties (walking one block, climbing several flights of stairs, getting up from chair, stooping, extending arms, lifting 10 lbs, picking up dime), for a total of 18 difficulties covering a wide range of severity. A linear regression model will be used to predict the functional difficulty index at the next wave following the stressor (two-year timepoint). Independent variables will include the baseline functional difficulty index, frailty, age, sex, and history of events (heart attack or stroke). The expected recovery differential is calculated as the difference between the observed and expected functional difficulty index at the two-year timepoint. Following Colón-Emeric et al. (22), the highest and lowest quartiles will be used to indicate those who recovered faster (high resilience) and slower (low resilience) than expected, respectively. This will allow a designation of a high, medium, or low resilience for each event in the dataset. Since this strategy will allow for multiple events and resilience designations per person, if within-individual resilience status is observed to change over time, this can be further explored for associations.

Supervised Machine Learning Model

Extreme gradient boosting (XGBoost) (46) will be used to predict the classification of physical resilience for each event into high, medium and low, corresponding the top 25%, middle 50%, and bottom 25% of the expected recovery differential. These labels will be used independently of the stressor that generated them (i.e., heart attack or stroke), with the goal of predicting a non-specific, whole person physical resilience that cuts across multiple domains. XGBoost is a popular, efficient, scalable tree boosting system with strong performance for tabular data that has been used by numerous winning teams in Kaggle competitions (46). Hyperparameters will be tuned following the tuning strategy described by Boehmke and Greenwell (47).

Feature Engineering

HRS has a breadth of longitudinal demographic, health and other information (such as detailed information on spouse) to be used as features for the predictive model. A key point when selecting features will be to ensure only variables observed during the wave prior to the event will be used, as the prediction needs to be generalizable to those who have not yet experienced an event (thus, we would only have data prior to their hypothetical future events). Thus, all relevant prior longitudinal information will be collapsed into features observed the wave prior to the event. In addition to the breath of features readily available in HRS, additional relevant features will be generated in an attempt to improve model performance. Specifically, an indirect cross-sectional measure of resilience will be generated for each individual in each wave following the methods of Wu et al. 2019 discussed above (35). This method classifies individuals as adapters, expected agers, and premature frailers based on the frailty-disease burden mismatch. If this feature is independently predictive of functional recovery (as the original authors expect it to be), it should improve performance of our model.

Training and Evaluation Metrics

The HRS data will be split to 70% training and 30% testing. 5-fold cross-validation will be used on the 70% training set to reduce overfitting, and class weights will be used to compensate for imbalanced training data. Evaluation metrics will include misclassification, mean-squared error, sensitivity, and specificity.

Imputation of Physical Resilience in Those Who Have Not Experienced a Stressor

Providing our model has adequate performance metrics, physical resilience will be imputed in the entire HRS sample, regardless of whether an individual has experienced a stressor. With this imputed data, the following analyses will be completed:

1. Descriptive analyses: determine population-wide patterns and distributions, and co-occurrence with frailty.
2. Determine if physical resilience independently predicts mortality after accounting for frailty
    - Logistic regression model predicting mortality using frailty, resilience, and potential confounders
3. Determine if physical resilience modifies the effect of frailty on mortality risk
    - Stratified logistic regression models predicting mortality using frailty and potential confounders (stratified by level of physical resilience).

If our model has inadequate performance, these analyses will be performed without imputation, exclusively on those individuals who have experienced a heart attack or stroke.

Budget and Timeline

The proposed project will take place over 1 full calendar year (July 1st 2022, to June 30th 2023), with an estimated budget of $28,909.40 (Table 1).

Table 1. Budget Justification

Expense	Amount	Justification
Doctoral student stipend	$20,000.00	Nathan Smith, a doctoral candidate in the department of Community Health and Epidemiology will complete the proposed project over the course of a year. The department requests a minimum about of $20,000 per year for a doctoral student stipend.
Laptop computer	$1,500.00	A laptop in this price range will be able to handle all computational requirements with the following specifications: Lenovo IdeaPad 5 15.6" Laptop - Abyss Blue (AMD Ryzen 7 5700U/512GB SSD/16GB RAM/Windows 11) | Best Buy Canada.
Conference	$2,100.00	$600 for registration, $150 for meals ($50 per diem x 3 days), $150 for ground transportation, $600 for accommodations ($200 x 3 nights), $600 for flight (estimate for a domestic flight; destination city not yet chosen). The Canadian Geriatrics Society - Conferences (wildapricot.org)
Publication fee	$5,309.40	Open access publishing fee for The journals of Gerontology Series A. Non-member price is $4076 USD = $5309.40 CAD @ 1.30:1 (exchange rate as of June 18th 2022). Charges | Journals | Oxford Academic (oup.com).
Total	$28,909.40	

Estimated one-year timeline for proposed project:

- Data analysis: July 1st, 2022 – January 31st, 2023
- Manuscript preparation: February 1st, 2023 – April 30th, 2023
- End of project knowledge translation: May 1st, 2023 – June 20th, 2023

Ethics

As this study will exclusively involve secondary use of publicly available data, it is exempt from research ethics board review as outlined in the Tri-Council Policy Statement (TCPS) Article 2.2. (48). Publicly available datasets have been de-identified to pose minimal risk to participant privacy, and thus there are no anticipated harms due use of sensitive participant information in this project.

One potential concern this project could pose is the discriminatory use of this method to identify high-risk individuals (who may not have previously been considered high risk). For example, if an insurance company used this approach to charge higher insurance premiums to those at highest risk, or perhaps even deny coverage. However, this approach would simply augment/improve current approaches where frailty assessments take place, and so this is not expected to be an issue. I believe the proposed benefits strongly outweigh the unlikely potential harms.

The research team have no conflicts of interest to declare.

Discussion

Implications

When complete, this project has the potential to offer conceptual, methodological, and empirical advances to the field of aging. Specifically, this project has the potential to offer 1) further evidence supporting an underlying non-specific resilience trait, 2) a new approach to determine physical resilience before an individual has experienced a stressor, 3) the first population-level description of distributions of physical resilience, and 4) the first in-depth comparison of frailty and physical resilience to help guide and refine the discourse in the field. Ultimately, if this project can determine if resilience independently predicts mortality, and/or modifies the effect of frailty, this would provide support for recent conceptual discourse advocating for the use of both concepts in the assessment of older adults, and would support the adoption of this measure in routine assessment (as is done with frailty right now). Further, this would improve identification of at-risk groups and individuals for targeted intervention. Alternatively, if the results indicate that the degree of overlap between frailty and physical resilience is so substantial that physical resilience provides little benefit beyond what frailty has to offer, this would also be important to inform the discourse and perhaps cool the recent excitement of physical resilience.

Potential Challenges and Limitations

Though this study has significant potential to contribute to the science of aging, there are a number of potential challenges and limitations. First, HRS may not have the temporal resolution to adequately capture resilience, as data is collected every two years. This is a longer-term recovery window than the majority of literature reviewed in this proposal. However, if this longer timeframe is able to capture the expected recovery differential for heart attack and stroke, this would contribute unique knowledge. Further, only using heart attack and stroke as stressors may limit the generalizability of this approach to cardiovascular stressors. It is possible that this does not cover a wide enough range of stressors to accurately estimate a truly non-specific whole person resilience that cuts across *all* domains. Unfortunately, these are the only major health stressors with exact timing in the HRS dataset other than cancer. However, the type of cancer is not recorded. This heterogenous variable would likely cause issues when estimating the expected recovery differential, as different types of cancer can have drastically different progression and recovery. There is also the possibility that the machine learning model will not be able to achieve performance. In this case, the secondary analyses will be carried out without imputation, and can still provide benefit to the field on a smaller scale. And lastly, given that HRS is a US dataset, the results generated here will not be generalizable to other countries.

Future work

There is ample opportunity to expand upon the proposed project once complete. Such opportunities include 1) applying this approach to HRS sister studies to allow a comparative analysis of different countries, 2) apply this approach to electronic medical record data for a clinical rather than population-based application, 3) apply this approach to short-term recovery with higher temporal resolution data, 4) a comparison/evaluation of indirect resilience measures, 5) further examination of the most important predictive features, and 6) explore model improvement in data with better temporal resolution, and with more stressors and outcomes to predict the expected recovery differential.

Knowledge Translation

As this research is aimed at improving our ability to accurately estimate resilience, and gleaming a deeper understanding of this concept itself, this research area is still in the formative stages. As such, the most relevant stakeholders for this research are primarily aging researchers and clinicians.

Knowledge translation for the proposed project will take an integrated approach, engaging with relevant stakeholders throughout the development and conduct of the research rather than simply communicating results once the research has been completed. This will ensure a two-way exchange of information by sharing ideas and updates with stakeholders, allowing us to incorporate their input and feedback to ensure the project produces relevant, useful results. To do this, the project team will engage with frailty research groups and other aging researchers throughout the course of the project. This will take the form of attending and giving presentations with local groups within Dalhousie (such as the Rockwood frailty group, whom invented the Frailty Index), as well as networking with other researchers in related areas of study from other institutions. In addition, the team will explore engagement in online mediums, where researchers can share and discuss ideas such as Twitter and Research Gate.

When the project is complete, the results will be written up in a manuscript to be submitted to a relevant peer-reviewed journal, such as the Journal of the American Geriatric Society, or Journals of Gerontology Series A-Biological Sciences and Medical Sciences. I plan to publish as open access to enable wide access and dissemination without financial barriers. When published, the team will promote the research by sharing an easy-to-understand graphical abstract and full text link with online networks (e.g., Twitter & Research Gate). I will also present the results at a national conference such as the Canadian Geriatrics Society Conference 2023, and continue our ongoing engagement with relevant stakeholders to help shape the next steps of this research.

References

1. Statistics Canada. Older adults and population aging statistics. [Internet]. 2022 [cited 2022 Jun 18]. Available from: https://www.statcan.gc.ca/en/subjects-start/older_adults_and_population_aging

2. Morley JE, Haren MT, Rolland Y, Kim MJ. Frailty. Medical Clinics. 2006;90(5):837–47.

3. Theou O, Brothers TD, Mitnitski A, Rockwood K. Operationalization of Frailty Using Eight Commonly Used Scales and Comparison of Their Ability to Predict All-Cause Mortality. J Am Geriatr Soc. J Am Geriatr Soc 61:1537-1551, 2013. 2013;61(9):1537–51.

4. op het Veld LPM, Beurskens AJHM, de Vet HCW, van Kuijk SMJ, Hajema K, Kempen GIJM, et al. The ability of four frailty screening instruments to predict mortality, hospitalization and dependency in (instrumental) activities of daily living. European journal of ageing. 2019;16(3):387–94.

5. Gonzalez-Colaço Harmand M, Meillon C, Bergua V, Tabue Teguo M, Dartigues JF, Avila-Funes JA, et al. COMPARING THE PREDICTIVE VALUE OF THREE DEFINITIONS OF FRAILTY: RESULTS FROM THE THREE-CITY STUDY. Arch Gerontol Geriatr. 2017;72:153–63.

6. Si H, Jin Y, Qiao X, Tian X, Liu X, Wang C. Predictive performance of 7 frailty instruments for short-term disability, falls and hospitalization among Chinese community-dwelling older adults: A prospective cohort study. Int J Nurs Stud. 2021;117:103875–103875.

7. Andrew M, Searle SD, McElhaney JE, McNeil SA, Clarke B, Rockwood K, et al. COVID-19, frailty and long-term care: Implications for policy and practice. The Journal of Infection in Developing Countries. 2020;14(05):428–32.

8. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical resilience in older adults: systematic review and development of an emerging construct. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2016;71(4):489–95.

9. Hadley EC, Kuchel GA, Newman AB. Report: NIA workshop on measures of physiologic resiliencies in human aging. The Journals of Gerontology: Series A. 2017;72(7):980–90.

10. Chhetri JK, Xue QL, Ma L, Chan P, Varadhan R. Intrinsic capacity as a determinant of physical resilience in older adults. The journal of nutrition, health & aging. 2021;25(8):1006–11.

11. Gijzel SM, Whitson HE, van de Leemput IA, Scheffer M, van Asselt D, Rector JL, et al. Resilience in clinical care: getting a grip on the recovery potential of older adults. Journal of the American Geriatrics Society. 2019;67(12):2650–7.

12. Varadhan R, Walston JD, Bandeen-Roche K. Can a Link Be Found Between Physical Resilience and Frailty in Older Adults by Studying Dynamical Systems? Journal of the American Geriatrics Society. 2018;66(8):1455–8.

13. Kuchel GA. Frailty and resilience as outcome measures in clinical trials and geriatric care: are we getting any closer? Journal of the American Geriatrics Society. 2018;66(8):1451.

14. Whitson HE, Cohen HJ, Schmader K, Morey MC, Kuchel G, Colon-Emeric C. Physical resilience: not simply the opposite of frailty. Journal of the American Geriatrics Society. 2018;66(8):1459.

15. Olde Rikkert MG, Melis RJ. Rerouting geriatric medicine by complementing static frailty measures with dynamic resilience indicators of recovery potential. Frontiers in physiology. 2019;10:723.

16. Whitson HE, Crabtree D, Pieper CF, Ha C, Au S, Berger M, et al. A template for physical resilience research in older adults: Methods of the PRIME-KNEE study. Journal of the American Geriatrics Society. 2021;69(11):3232–41.

17. Presley CJ, Arrato NA, Shields PG, Carbone DP, Wong ML, Benedict J, et al. Functional Trajectories & Resilience among Adults with Advanced Lung Cancer. JTO Clinical and Research Reports. 2022;100334.

18. Pedone C, Costanzo L, Finamore P, Bandinelli S, Ferrucci L, Antonelli Incalzi R. Defining resilience in older people: does a subjective definition of stressor work? The Journals of Gerontology: Series A. 2021;76(8):1480–5.

19. Calle A, Onder G, Morandi A, Bellelli G, Ortolani E, Pérez L, et al. Frailty related factors as predictors of functional recovery in geriatric rehabilitation: the sarcopenia and function in aging rehabilitation (SAFARI) multi-centric study. The journal of nutrition, health & aging. 2018;22(9):1099–106.

20. Duan-Porter W, Cohen HJ, Demark-Wahnefried W, Sloane R, Pendergast JF, Snyder DC, et al. Physical resilience of older cancer survivors: an emerging concept. Journal of geriatric oncology. 2016;7(6):471–8.

21. Colón-Emeric C, Whitson HE, Pieper CF, Sloane R, Orwig D, Huffman KM, et al. Resiliency Groups Following Hip Fracture in Older Adults. Journal of the American Geriatrics Society. 2019;67(12):2519–27.

22. Colón-Emeric C, Pieper CF, Schmader KE, Sloane R, Bloom A, McClain M, et al. Two approaches to classifying and quantifying physical resilience in longitudinal data. The Journals of Gerontology: Series A. 2020;75(4):731–8.

23. Rector JL, Gijzel SM, van de Leemput IA, van Meulen FB, Rikkert MGO, Melis RJ. Dynamical indicators of resilience from physiological time series in geriatric inpatients: Lessons learned. Experimental Gerontology. 2021;149:111341.

24. Parker DC, Colón-Emeric C, Huebner JL, Chou CH, Kraus VB, Pieper CF, et al. Biomarkers associated with physical resilience after hip fracture. The Journals of Gerontology: Series A. 2020;75(10):e166–72.

25. Resnick B, Galik E, Dorsey S, Scheve A, Gutkin S. Reliability and validity testing of the physical resilience measure. The Gerontologist. 2011;51(5):643–52.

26. Park J, Lee J, Lee H, Kim S, Kim CO, Park CG. Physical resilience as a moderator of the relationship between frailty and disability in older adults with osteoarthritis. Journal of Advanced Nursing. 2022;

27. Hu FW, Lin CH, Lai PH, Lin CY. Predictive Validity of the Physical Resilience Instrument for Older Adults (PRIFOR). The journal of nutrition, health & aging. 2021;25(9):1042–5.

28. Hu FW, Lin CH, Yueh FR, Lo YT, Lin CY. Development and psychometric evaluation of the Physical Resilience Instrument for Older Adults (PRIFOR). BMC geriatrics. 2022;22(1):1–10.

29. Gijzel SM, van de Leemput IA, Scheffer M, Roppolo M, Olde Rikkert MG, Melis RJ. Dynamical resilience indicators in time series of self-rated health correspond to frailty levels in older adults. The Journals of Gerontology: Series A. 2017;72(7):991–6.

30. Gijzel SM, van de Leemput IA, Scheffer M, van Bon GE, Weerdesteyn V, Eijsvogels TM, et al. Dynamical indicators of resilience in postural balance time series are related to successful aging in high-functioning older adults. The Journals of Gerontology: Series A. 2019;74(7):1119–26.

31. Gijzel SM, Rector J, van Meulen FB, van Der Loeff RS, van de Leemput IA, Scheffer M, et al. Measurement of dynamical resilience indicators improves the prediction of recovery following hospitalization in older adults. Journal of the American Medical Directors Association. 2020;21(4):525–30.

32. Kolk D, Melis RJ, MacNeil-Vroomen JL, Buurman BM, Reichardt LA, Aarden J, et al. Physical Resilience in Daily Functioning Among Acutely Ill Hospitalized Older Adults: The Hospital-ADL Study. Journal of the American Medical Directors Association. 2022;23(5):903-e1.

33. Zhu Y, Chen X, Geng S, Li Q, Yuan H, Zhou X, et al. Association between ambulatory blood pressure variability and frailty among older hypertensive patients. The Journal of Clinical Hypertension. 2020;22(9):1703–12.

34. Rouch L, De Souto Barreto P, Hanon O, Vidal JS, Amar J, Andrieu S, et al. Visit-to-visit blood pressure variability and incident frailty in older adults. The Journals of Gerontology: Series A. 2021;

35. Wu C, Li YX, Marron MM, Odden MC, Newman AB, Sanders JL. Quantifying and Classifying Physical Resilience Among Older Adults: The Health, Aging, and Body Composition Study. The Journals of Gerontology: Series A. 2019;

36. Sotos-Prieto M, Ortolá R, López-García E, Rodríguez-Artalejo F, García-Esquinas E. Adherence to the Mediterranean diet and physical resilience in older adults: The Seniors-ENRICA Cohort. The Journals of Gerontology: Series A. 2021;76(3):505–12.

37. Belsky DW, Caspi A, Houts R, Cohen HJ, Corcoran DL, Danese A, et al. Quantification of biological aging in young adults. Proceedings of the National Academy of Sciences. 2015;112(30):E4104–10.

38. Belsky DW, Caspi A, Cohen HJ, Kraus WE, Ramrakha S, Poulton R, et al. Impact of early personal-history characteristics on the Pace of Aging: implications for clinical trials of therapies to slow aging and extend healthspan. Aging Cell. 2017;16(4):644–51.

39. Li X, Ploner A, Wang Y, Magnusson PK, Reynolds C, Finkel D, et al. Longitudinal trajectories, correlations and mortality associations of nine biological ages across 20-years follow-up. Elife. 2020;9:e51507.

40. Arbeev KG, Ukraintseva SV, Bagley O, Zhbannikov IY, Cohen AA, Kulminski AM, et al. "Physiological Dysregulation" as a promising measure of robustness and resilience in studies of aging and a new indicator of preclinical disease. The Journals of Gerontology: Series A. 2019;74(4):462–8.

41. Galvin A, Ukraintseva S, Arbeev K, Feitosa M, Christensen K. Physical robustness and resilience among long-lived female siblings: a comparison with sporadic long-livers. Aging. 2020;12(14):15157–68.

42. Weir DR. Validating mortality ascertainment in the health and retirement study. Ann Arbor, Michigan: Survey Research Center, Institute for Social Research, University of Michigan. 2016;

43. Heeringa SG, Connor JH. Technical description of the Health and Retirement Survey sample design. Ann Arbor: University of Michigan. 1995;

44. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC geriatrics. 2008;8(1):24.

45. Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. Mechanisms of ageing and development. 2006;127(5):494–6.

46. Chen T, Guestrin C. Xgboost: A scalable tree boosting system. In 2016. p. 785–94.

47. Boehmke B, Greenwell B. Hands-on machine learning with R. Chapman and Hall/CRC; 2019.

48. Canadian Institutes of Health Research, Natural Sciences and Engineering, Research Council of Canada, and Social Sciences and Humanities Research, Council. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 2018.

Appendix

Table S1. Summary of the Empirical Literature Measuring Physical Resilience

Operationalization of Resilience	Stressor	Outcome Measure	Time Scale	Sample Size	References
Direct					
Categorization based on observed decline (resilient, non-resilient, decliners)	Non-specific "major health event"	Short physical performance battery (SBBP)	Baseline plus follow-up at three years after baseline, with or without a major health event in between.	726 for mortality outcome, 567 for functional status outcome	Pedone 2020 (18)
Relative and absolute functional gain (AFG, RFG)	Specific	Barthel Index	Baseline plus 2 measurements with 30 days in between	450	Calle 2018 (19)
Maintenance or improvement in disability scores	Specific		Monthly for 8 months	207	Presley 2022 (7)
Recovery Phenotype – LCA using multiple outcomes to determine high, medium, and low resilience OR use PCA for multiple classification variables	Specific	LCA of Self-reported physical function for hip fracture EQ-5D-5L (for pneumonia a variety of factors such as length of hospital stay, ICU admission)	Baseline, 2, 6 and 10 months for hip fracture. 28 days for pneumonia	541 541 hip fracture, 185 pneumonia	Colón-Emeric 2019 (6), Colón-Emeric 2020 (8)
Expected Recovery Differential (expected vs observed based on population)	Specific	Self-reported physical function (for pneumonia a variety of factors such as length of hospital stay, ICU admission)	4 observations in 10 months	541 hip fracture, 185 pneumonia	Colón-Emeric 2020 (8), Parker 2020 (9)
Regaining at least 50% of lost function after decline	Specific	SF-36 physical function subscale	Quarterly over two years	594	Duan-porter 2016 (10)
Indirect					

The Physical Resilience Instrument	No	Questionnaire	Cross-sectional	130 235	Resnick 2011 (4), Park 2022 (5)
PRIFOR	No	Questionnaire	Cross-sectional	192 200	Hu 2021 (2), Hu 2022 (3)
DIOR – variance, cross-correlation, and temporal autocorrelation	No	Self-rated physical, mental, and social health, postural balance	30 second continuous feed for postural balance, daily for 100 days with self-rated	22 212 121	Gijzel 2017 (11), Gijzel 2019 (12), Gijzel 2020 (13)
DIOR: CSD and LoC	No	Heart rate and physical activity	11 hours of recording	121	Rector 2021 (14)
DIOR: variance	No	step count, self-rated levels of pain, fatigue, fear of falling. Coefficient of variation for DIOR rather than SD	3 months of observations- continuous for steps, daily for self-rated measures. Minimum of three days of observations	of 207	Kolk 2021 (15)
Mismatch between frailty and disease burden: adapters, expected agers, premature frailers	No	Residuals of linear regression Follow up simplified approach	Cross-sectional	2,457 2,457	Wu 2019 (20), Wu 2022 (21)
Resilience defined as accumulated fewer deficits than expected	No	52 item “deficit accumulation index” – essentially FI	Cross-sectional	1301	Sotos-Prieto 2021 (22)
Proxy measures: onset of “unhealthy life” and survival following onset/avoid diseases at age 65+, and survival to extreme ages	No	Unhealthy life: first occurrence of a major complex disease including cancer, CVD, and type II diabetes.	2-year resolution for Framingham and 1 year for CHS. Followed for many years	Framingham Cohort 5079, Cardiovascular Health Study 5795 1156	Arbeev 2019 (16), Galvin 2020 (17)