HDFS 649: Multidisciplinary Gerontology

Old Age Frailty: Mechanisms, Antecedents, and Mortality Outcomes

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1 Introduction

Broadly defined, frailty is characterised by the decline in physiological systems, and one's ability to regulate stressors [Yang et al., 2024]. Much scholarly focus in recent years have turned increasingly towards elderly frailty, in view of population ageing induced by the demographic transition. Specifically, declining death rates (e.g., due to the advancement of medical technology and prolonged lifespans) coupled with falling birth rates have contributed to a population structure comprised increasingly by older individuals. This has given rise to concerns that an increasing proportion of populations will become susceptible to frailty, which is often treated as a function of chronological ageing.

Growing incidences of frailty produce concern at both the individual- and aggregate-levels. At the individual level, frailty has consistently been shown to be a robust predictor of various deleterious health outcomes. Relative to non-frail individuals, epidemiologists demonstrate that frailty is associated with $1.8 - 2.3$ folds the risk of mortality; $1.6 - 2.0$ folds the risk of being unable to engage in daily activities; $1.2 - 1.8$ folds the risk of hospitalisation; as well as other negative health outcomes [Vermeiren et al., 2016; Forti et al., 2014, 2012; Woo et al., 2012]. Beyond physical health, frailty is also related to severe mental illness. Systematic reviews show that frailty among older adults is associated with overall higher rates of cognitive deficits, schizophrenia, bipolar disorder, depression, and other deleterious mental health outcomes [Pearson et al., 2022; Schmahl et al., 2021; Aliño-Dies et al., 2020; Alyazidi et al., 2018].

On a macro-level, fraility, and population ageing more generally, is linked to an increased need for healthcare- and other kinds of economic support. Population-level studies currently estimate the prevalence of frailty among 62 countries to be around 7% to 24%, depending on how frailty is operationalised [O'Caoimh et al., 2021]. Health economists suggest that the economic 'burden' of frailty comprises approximately 40% to 76% of total healthcare costs annually [Alkhodary et al., 2020]. In matching non-frail controls to frail patients, total healthcare costs for the exposed group was approximately 44% more than that incurred by non-frail individuals. From a demographic perspective, such excess costs of frailty impose a heavier financial burden on the working population, in addition to the already rising old-age dependency ratio[1] due to ageing population structure. Beyond financial costs, a growing proportion of frail patients may also confer greater psychological stress on caretakers, given positive associations between care-taking duties of frail individuals and moderate to severe psychological distress [Abreu et al., 2020]. The growing prevalence of frailty, as well as the costs imposed on the economy and caretakers, therefore marks a burgeoning concern for public health researchers.

[1] Old age dependency ratio is taken as the proportion of old age individuals above 65 years old relative to the working-age population

While policymakers have devoted much effort to devise policies aimed at offsetting the healthcare and economic burden of frailty (e.g., expanding the informal care industry; prolonging retirement ages), recent studies have turned their attention to the upstream antecedents of frailty. Re-centering the focus towards upstream factors is important because it maximises the potential for preventive –rather than reactive– policy interventions to alleviate frailty within the population [Herd et al., 2011]. One dominant strand of research examines the role of childhood and adulthood adversity, which have consistently between associated with deleterious later-life outcomes [Aas et al., 2020; Belsky et al., 2017; Boyes et al., 2016; Carpenter et al., 2009; Agid et al., 1999]. This paper therefore reviews recent literature examining how adversities influence frailty in old age from a life course perspective.

In this paper, I first outline prominent conceptual models of frailty, and how this manifests in different operationalisations of frailty. I then highlight three overarching (biological) mechanisms of frailty commonly discussed in the literature. Finally, I discuss the effects of life course adversity on frailty, and subsequent consequences of frailty on mortality.

2 Operationalising Frailty and Conceptual Models

Existing studies elucidate three pertinent conceptual models of frailty: *reliability theory*; *allostatic load*; and *complexity theory*. I elaborate on each model below.

2.1 Reliability theory

Reliability theory posits that human beings possess a finite number of redundant biological systems and resources to maintain homeostasis[2]. Yet ageing, as well as exposures to deleterious encounters, deplete such resources through a process of *deficit accumulation* involving (but not limited to) genetic damage, bodily stress, and comorbidities throughout one's lifetime [Zaslavsky et al., 2012]. Taking this view, some studies conceptualise of frailty in terms of the extent of accumulated age-related deficits and ailments across various physiological systems experienced by an individual. Such deficits first arise at subcellular levels, which then affect higher-order function –such as tissues, organs, and integrated organ action– and ultimately culminating in age-related diseases [Rockwood and Mitnitski, 2012].

Indeed, existing studies also provide support for this view, finding evidence of age-related negative exposures being linked to declines in cumulative cell loss and other

[2]Homeostasis refers to the ability of an organism or cell to maintain a stable internal environment in the face of fluctuating external conditions to ensure survival.

homeostatic mechanisms [Wallace and Kelsey, 2010; Andersen et al., 2003; Leeuwenburgh, 2003]. Cumulative deficits at the subcellular level, for instance, have been found to be associated with a heightened risk of diabetes mellitus and Alzheimer's disease by impinging on individuals' glucose metabolism [Gerozissis, 2010]. Individuals who died before age 75 and after age 85 also expressed similar profiles of cumulative deficits across their lifespan, suggesting strong support for the reliability theory.

In this perspective, frailty is therefore expressed as a frailty index (FI) which sums up individual deficits at the point of evaluation, divided by the total number of symptoms, signs, and impairments measured. Frailty is therefore quantified by age-related changes across physiological, psychological and functional conditions among the elderly, and expressed as a continuous value from zero to one [Bouillon et al., 2013; Searle et al., 2008; Rockwood et al., 2007; Mitnitski et al., 2001]. A second operationalisation of frailty pertains to Rockwood's Clinical Frailty Scale (CFS), which categorises individuals into seven categories based on physiological functioning across domains of disease pathology, physical activity, ability to engage in daily activities, and need for caretaking [Rockwood et al., 2007].

2.2 Allostatic Load

Unlike the reliability theory which posits an accumulative model of frailty, frailty conceived as the build-up of allostatic load adopts a threshold model of frailty. That is, individuals suffer a greater risk of age-related diseases and other adverse outcomes beyond a level (i.e., the threshold) of allostatic load build-up. More precisely, allostatic load refers to the 'wear and tear' of physiological systems which ultimately result in dysfunction beyond a certain level.

Evidence in favour of allostatic load theory finds that allostatic load are predictive of physiological problems in both cross-sectional and longitudinal studies [Zaslavsky et al., 2012; Szanton et al., 2009]. For instance, declines in muscle strength and oxidative stress levels –markers of allostatic load– have been linked to inflammation and endocrine misbalance [Polidori and Mecocci, 2022; Farrow et al., 2021; Batista et al., 2012; Schaap et al., 2009]. Similarly, a prospective study discovered a correlation between the abnormal levels of allostatic load and symptoms of age-related disease, establishing support for allostatic load as a proxy for frailty [Gruenewald et al., 2009].

Studies in line with this framework operationalise frailty in terms of five criteria outlined in the Fried et al's frailty scale: a) unintentional weight loss that is greater than 4.5 kg or over 5% of body weight in the last year; b) fatigue levels; c) reductions in grip strength after adjusting for gender and body mass index ; d) having low levels of physical activity in terms of weekly energy expenditure, measured through domestic activities

and physical exercises; e) low gait speed measured through time taken by elderly persons to travel a distance of 4.5 metres in a straight line with usual gait [Fried et al., 2001]. Elderly persons with three or more of the above phenotypes are considered frail, while those with one or two components are classified as pre-frail [Fried et al., 2001]. Recent studies have however also focused on finer indicators of allostatic load, integrating various biomarkers of cardiovascular, metabolic, endocrine, and inflammatory regulatory systems to construct an allostatic load index quantifying the wear and tear on the body [Dowd et al., 2024; Ding et al., 2019; Dowd et al., 2009].

2.3 Complexity Theory

Complexity theory focuses on the interaction between biological systems to produce compensatory mechanisms that counteract accumulated physiological abnormalities [Lipsitz, 2004]. In this view, impaired interactions between physical systems compromise individual ability to mount bodily adaptations in response to stressors, resulting in a greater vulnerability during old age [Chaves et al., 2008]. Few research has however attempted to leverage this concept in measuring frailty. Among existing studies, scholars have proposed a range of biomarkers as indicators of an impaired interaction between biological systems. The key metric frequently used relates to heart rate variability, which refer to the natural variation in the intervals between heart beats. Conceptually, heart rate variability reflect the interaction between biological systems through the exchange of regulatory signals to maintain cardiovascular homeostasis [Zaslavsky et al., 2012]. Indeed, studies have found the regularity of heart rate fluctuations to be highly associated with old age [Beckers et al., 2006], as well as greater morbidity and mortality [Mäkikallio et al., 2004].

3 Mechanisms of Frailty

While much effort has been dedicated to conceptualise and operationalise frailty, limited research has examined the mechanisms underlying the dynamic nature of this condition and its development throughout the life course. Existing studies primarily point to mechanisms operating at three different levels of the biological system: *cellular changes*; *system dysregulation*; and *system impairment*.

3.1 Cellular Changes

Among cellular-related mechanisms, oxidative stress has received extensive attention as a (bio)marker indicative of frailty in old age. Existing evidence largely agree that altered oxidative stress constitutes a plausible pathway towards physical and cognitive frailty

across different populations [Bourg et al., 2021; Sargent et al., 2018; Saum et al., 2015; Walston, 2004]. In particular, reactive oxygen species –molecules generated during enzymatic reactions– may produce deleterious oxidising effects within proteins, DNA and lipids [Álvarez-Satta et al., 2020]. The degree to which this happens is quantified through varying levels of oxidative stress, and is commonly established to be a primary pathophysiological mechanism underlying ageing-related diseases.

Indeed, various biomarkers indicative of oxdiative stress have been found to be strongly correlated and associated with frailty. An increased lipoprotein-associated phospholipase A2 (Lp-PLA2) expression in blood was detected for instance, among the frail rather than non-frail population within the Framingham Offspring Study [Liu et al., 2016]; whereas frailty was also found to be significantly correlated with increased levels of urinary 8-isoprostane – another biomarker of oxidative stress [Syslová et al., 2014]. Similar associations were detected between frailty in old age and other oxidative stress biomarkers, including but not restricted to the 8-hydroxy-2'-deoxyguanosine (8-OHdG); derivatives of reactive oxygen metabolites (d-ROM), and levels of carbonylated circulating proteins [Namioka et al., 2017; Hirata et al., 2015; Saum et al., 2015; Inglés et al., 2014; Wu et al., 2009; Howard et al., 2007; Semba et al., 2007].

In recent years, further evidence indicates the increased role played by intermediate factors along the causal chain. Saum et al. [2015], for instance, finds the effect of d-ROM production on frailty to be highly attenuated after controlling for the development of age-related diseases. Noting that the overproduction of d-ROM is highly central to the incidence of age-related diseases [Khansari et al., 2009], it is therefore possible that much of the effects of oxidative stress on frailty is mediated through age-related diseases.

3.2 System Dysregulation

Beyond the cellular level, other studies have examined other possible higher level pathways contributing to old age frailty. Key to such research are findings relating to *inflammatory pathway dysregulation, endocrine dysregulation*, and *metabolic dysregulation*.

3.2.1 Inflammatory Pathway Dysregulation

Earlier studies have found elevated levels of inflammation in frail rather than non-frail individuals across age-matched counterparts [Álvarez-Satta et al., 2020; Chen et al., 2014; Khansari et al., 2009]. In comparing C-reactive protein (CRP) –an established biomarker of inflammation– within subjects, individuals with elevated levels of CRP had about 3 folds the odds of being frail in old age [Saum et al., 2015]. Subsequent meta-analysis similarly concurrred with such findings, demonstrating that both frail and pre-frail par-

ticipants had significantly higher levels of CRP compared to robust participants [Soysal et al., 2016].

Similarly, serum levels of interleukin 6 (IL-6) were found to be starkly higher in frail elders (4.4 ± 2.9 pg/mL) compared to non-frail elders (2.8 ± 1.6 pg/mL) [Leng et al., 2002]. In particular, inflammation and tissue injuries result in the production of IL-6, where it exerts multiple pleiotropic effects at the liver, such as the production of CRP highlighted earlier [Cardoso et al., 2018]. Subsequent analyses comprising larger sample sizes replicated this result, finding higher serum levels of IL-6 in both frail and pre-frail individuals compared to robust subjects [Chen et al., 2014; Reiner et al., 2009]. Results were consistent in the most recent meta-analysis examining the relationship between IL-6 and frailty, with frail (standardised mean difference = 1.12) and pre-frail (standardised mean difference = 0.56) participants having higher serum levels of IL-6 compared to robust individuals [Soysal et al., 2016]. Research on other biomarkers have found similar results identifying inverse correlations between frailty and other bio-indicators of inflammation, such as weak androgenic steroid dehydroepiandrosterone sulfate (DHEA-S) linked to muscle mass maintenance; and insulin-like growth factor 1 (IGF-1) crucial to muscle mass maintenance and life span regulation [Walston, 2004].

3.2.2 Endocrine dysregulation

Apart from inflammation, frailty is also thought to result from alterations in anabolic hormones, given the effect of endocrine dysregulation on biological senescence [Zaslavsky et al., 2012]. In particular, anabolic hormones have been established as a key factor underlying muscle growth and repair, which is in turn heavily linked to frailty status [Swiecicka et al., 2017]. Existing cross-sectional studies have largely discovered direct associations between anabolic hormones and frailty status. Tajar et al. [2013] found frailty status to be linked to various constituents of the vitamin D endrocrine axis. Specifically, individuals with low levels of vitamin D were associated with greater odds of developing frailty; while higher levels of parathyroid (PTH) hormones were linked to greater odds of being frail in old age [Tajar et al., 2013]. In a separate study, frailty was also found to be associated with lowered levels of anabolic hormones like insulin-like growth factor-I (IGF-I) and testosterone [Yeap et al., 2013], though results are inconsistent across other studies [Cawthon et al., 2009; Mohr et al., 2007] potentially due to varying social/environmental contexts adopted in cross-sectional studies. One prospective longitudinal study have found support for some of the above findings: elevated levels of IGF-I and vitamin D had protective effects against frailty risk, but no effects were detected for PTH [Swiecicka et al., 2017]. More longitudinal research is therefore crucial to address the validity of earlier findings.

3.2.3 Metabolic dysregulation

A third and prominent strand of research relates to metabolic dysregulation, which is commonly associated with insulin resistance syndrome. Insulin resistance (IR) constitutes a core area extensively studied by scholars because it is found to impair glucose uptake by skeletal muscle, thus contributing to greater chances of frailty [Mauk, 2017]. Adopting a prospective cohort study, increased insulin resistance (and metabolic syndrome) demonstrated an increased risk of frailty [Pérez-Tasigchana et al., 2017]. This echoed findings by earlier studies [Abbatecola and Paolisso, 2008; Barzilay et al., 2007]. Adopting a deficit accumulation model, a recent study further demonstrated that having long-term insulin resistance (i.e., a high IR trajectory) was significantly related to a greater prevalence of frailty even when compared to a moderate IR trajectory, highlighting the cumulative burden imposed by long-term health conditions [Ke et al., 2024].

Beyond insulin resistance, symptoms of metabolic dysregulation such as hyperglycemia was also tied directly to frailty status. Having hyperglycemia (measured through hemoglobin A1c) is associated with a greater likelihood of prefrail and frail status [Blaum et al., 2009]. Hyperglycenmia is furthermore proposed to drive the transition from pre-frail to frailty status, given observations that significantly more hyperglycemic patients developed frailty status compared to normoglycemic patients who remained pre-frail (40.2% vs 12.1%, $p < 0.001$) [Mone et al., 2023]. Findings therefore demonstrate a robust connection between metabolic dysregulation and frailty status.

3.3 System Impairment

Further considerations of *multisystem* impairment have also prompted research into higher order factors related to frailty development. Pertinent to this line of research are studies examining *musculoskeletal impairment* and *neurocognitive impairment*. I elaborate further below.

3.3.1 Musculoskeletal impairment

Frailty has largely been examined in relation to sarcopenia, commonly defined as a loss of muscle mass and strength. Older people are often at a higher risk of sarcopenia due to age-related declines in muscle functionality, which predisposes them to a broader range of adverse outcomes such as physical disability, frailty, and death [Cruz-Jentoft et al., 2010]. Because sarcopenia and frailty are often comorbid and tightly interlinked, sarcopenia is sometimes treated as a subset of the latter. But clinical criteria distinguishes between the two conditions: where sarcopenia refer to the loss of muscle mass and strength, frailty necessarily involves the loss of performance across various domains (e.g., exhaustion, low

physical activity, slowness etc) [Fried et al., 2001]. Nonetheless, whether or not sarcopenia and frailty represent similar conditions or distinct disorders linked by common etiologies remain a longstanding debate among scholars.

The dominant view makes the case for conceptual parsimony by treating sarcopenia and physical frailty as mutual indicators of each other, in view of the shared etiologies heavily established between both ailments [Cesari et al., 2014]. Shared etiologies between sarcopenia and frailty commonly include biological processes discussed above, including altered endocrine function, inflammation, insulin resistance, and oxidative stress mentioned earlier [Bollheimer et al., 2012; Volkert, 2011]. Other common etiologies commonly studied include one's nervous system function, muscle protein synthesis, malnutrition, and physical inactivity [Nascimento et al., 2019; Cruz-Jentoft et al., 2017; Varma et al., 2016; Viña et al., 2016; de Labra et al., 2015].

In contrast, few studies have attempted to investigate sarcopenia and frailty as distinct conditions. Among existing studies, scholars found that patients with sarcopenia have approximately 6.63–10.61 the odds of developing frailty [Davies et al., 2018]. In contrast to the earlier perspective then, the authors argue that the non-perfect correlation between both conditions suggest that sarcopenia and frailty are distinct, although related, conditions. Further support for this view is found in Laskou et al. [2022], whose cohort study found a positive, but not perfect, association between sarcopenia and the subsequent incidence of frailty ($OR = 8.28, p < 0.05$).

In addition to sarcopenia, research suggests that muscle mass loss is often accompanied by gains in fat mass. Parallel gains in muscle mass and loss of muscle mass often interact synergistically and contribute to sarcopenic obesity (SO). Early studies confirm that low muscle mass/density and high fat mass were indeed more prevalent among frail rather than non-frail subjects [Cesari et al., 2006]. SO diagnosis was associated with twice the odds of developing frailty, even after adjusting for low muscle mass and high fat mass [Hirani et al., 2017]. This suggests that synergistic effects of SO exert independent effects on frailty risk, over and beyond the effects exerted by muscle mass loss and fat gain individually. In contrast to this finding however, Ozkok et al. [2022] demonstrate that patients with SO were associated with a lower risk of frailty compared to those with just sarcopenia alone ($OR_{SO} = 5.9$, $OR_{sarcopenia} = 6.05$). Thus, it remains unclear if SO does indeed confer a higher risk of frailty onto patients compared to those with just sarcopenia or obesity per se.

3.3.2 Neurocognitive impairment

A plethora of studies have demonstrated positive associations between neurocognitive impairment and a range of frailty-linked functional declines. Neurocognitive impairment

has been examined across various dimensions, ranging from cognitive declines to sensory loss [Zaslavsky et al., 2012]. Impaired cognition for instance, positively predicted the onset of the frailty-related phenotypes such as functional decline, dementia, and hospitalisation ($RR = 1.9$) [Ávila-Funes et al., 2009]. Han et al. [2014] corroborate these results, further demonstrating that such effects do not differ between men and women. But the direction of such effects are less clear. Where the above (cross-sectional) studies suggest a detrimental effect of frailty on cognitive decline, other studies also demonstrate evidence for effects in the opposite direction. Meta-analysis find that baseline frailty was significantly associated with an increased risk of cognitive disorders ($OR = 1.8$) [Borges et al., 2019], while longitudinal studies also support findings of deleterious frailty effects on future cognitive decline [Auyeung et al., 2011].

Sensory loss was also found to be highly predictive of subsequent frailty status. Both vision and hearing loss was demonstrably related to a greater risk of frailty [Lorenzo-López et al., 2019; Ng et al., 2014], but smell impairment yielded mixed results. For instance, Laudisio et al. [2019] found olfactory dysfunction among an Italian population to be positively related to frailty ($OR = 1.94$), but non-significant effects were otherwise detected in a Japanese population by Somekawa et al. [2017]. Differences in these results may result from how smell perception was being measured, given that participants in the former study was only tested against three beverage items; but that of the latter being tested against six items. This implies that participants in the former are more likely than the latter to correctly 'guess' the food being presented, even if they were unable to accurate distinguish between the tested items. A recent meta-analysis appears to confirm these results: hearing and vision impairment was associated with 1.5–2 folds the odds of pre-frailty, and 2.5–3 folds the odds of frailty, while no results are detected for smelling loss [Tan et al., 2020].

4 Life Course Exposure to Adversity and Frailty

Research has found robust links between adversity and various deleterious outcomes, including poorer neurobiological health [Wade et al., 2022; Richards and Wadsworth, 2004], impaired educational development [Juwita et al., 2020; Sheridan and McLaughlin, 2016], and increased risk of frailty [Yang et al., 2024; Stenroth et al., 2023]. Much less studied is how the *life course exposure* to adversities affect such outcomes. That is, such studies do not often take into account how the timing, quantum, and recency of such exposures confer disadvantages onto its victims. Yet, distinguishing between these effects are crucial because it informs policymaking and maximises the intended effects of interventions. Whereas interventions are typically geared towards reducing the *cumu-*

lative exposure/risk of adversity for instance, Dunn et al. [2019] found that it is in fact adversities experienced at *sensitive developmental periods* (rather than the accumulative number of exposures) that exert the greatest impact on one's physical health. Below, I outline the various literature that examines links between adversity and frailty from a life course perspective.

4.1 Cumulative Risk

Within life course analysis, cumulative risk models suggest that the detrimental effects of adverse experiences compound as individuals become increasingly exposed to stressors over their life course. Recent research has provided some support that cumulative experiences of adversity exert a negative effect on frailty at older ages. Within the US for instance, Yang et al. [2024] demonstrated that every additional type of adversity accumulated over time is associated with an increased risk of frailty by 38%. Results in Canada yielded similar findings, with accumulated exposure to childhood adversity being associated with overall higher levels of frailty in older ages [Mian et al., 2021]. Findings are rather consistent across various countries, with cumulative adversity exposure being positively associated with greater risk of frailty in England, Netherlands, China, and Switzerland [Dimitriadis et al., 2023; Wang, 2023a,b; Van Der Linden et al., 2020]. Overarchingly, systematic reviews also provide evidence of increased frailty risk associated with accumulative adversity exposure [Tao et al., 2024].

One criticism of such life course studies is that scholars only examine particular life course models in isolation [Dunn et al., 2019]. In this view, results demonstrating a significant relationship between cumulative adversity exposure and frailty is treated as evidence in favour of a cumulative risk model. Yet, such significant results may cease to exist once other life course models (e.g., sensitive periods or recency) have been taken into account. To address such concerns, Baranyi et al. [2022] adopted a supervised learning approach to conduct feature selection among all competing life course models simultaneously. Their findings established further support for the cumulative risk model as the most salient predictor of frailty for boys. Specifically, accumulated exposure to socially deprived neighbourhoods –measured through multidimensional indexes of deprivation– at young ages was associated with higher baseline frailty for elderly men, but not women.

Indeed, studies suggest that cumulative adversity effects on frailty risk may differ between men and women. Some results suggest that women suffer from greater frailty risks [Tao et al., 2024]. For instance, moderate levels of lifetime adversity appeared to impact frailty risk only for women but not men [Wang, 2023a]. Women who suffered cumulative exposure to starvation were also at greater risk of frailty, but no effects were detected for men [Gao et al., 2022]. Furthermore, women with accumulated adversity demonstrated

not only higher risks, but also steeper trajectories of frailty [Tao et al., 2024; Wang, 2023a; Mian et al., 2021; Alvarado et al., 2008]. Results are not unanimous however. Bornscheuer et al. [2024] found little evidence of female-disadvantage in cumulative adverse experience; while contrasting evidence demonstrated that early life stress in Finland was associated with increased frailty risk among men but not women in Finland [Haapanen et al., 2018].

One possible explanation for such equivocal findings can be attributed to differences in social contexts wherein the study was conducted. In particular, female disadvantage was detected largely in neo-liberal nations (i.e., the US; Canada) rather than welfare regimes [Zhang et al., 2020; Homan, 2019; Cameron et al., 2010]. Females may then experience a health disadvantage because their weaker socioeconomic positions (on average) are associated with overall poorer health and healthcare access within liberal regimes [Coburn, 2004]. This contrasts with the relatively equitable healthcare utilisation in welfare states (e.g., Finland) [Isakjee, 2017; Kuhlmann and Annandale, 2015], for which differences in healthcare access across men and women may be less extreme than neo-liberal regimes. Indeed, Van Der Linden et al. [2020] demonstrated narrowing differences in frailty risk between individuals exposed to high and low levels of adversity over time in European welfare regimes, potentially signalling the utility of social support in minimising health disparities induced by lifetime stressors.

4.2 Sensitive Periods

Sensitive periods refer to specific ages during which stress or adversity exposure exerts a marked pronounced effect on individual behaviours and outcomes. Sensitive periods typically exist during early childhood due to elevated levels of brain plasticity in children developmental phases. Stressors or shocks experienced during developmental phases may modify neural circuits in ways that cause certain forms of connectivity patterns to become preferred [Knudsen, 2004]. Such preferred forms of neural connectivity induced in childhood then subsequently manifests in terms of behavioural choices, ostensibly resulting in disparate health outcomes. Evidence in support of the sensitive period hypothesis relates heavily to the *long arm of childhood* literature. Negative experiences during early childhood have been consistently found to be associated with much later outcomes, such as old age health and mortality [Pakpahan et al., 2017; Hayward and Gorman, 2004]. Longitudinally, poor childhood health and SES origins are also associated with a faster rate of functional health and cognitive declines [Tsang et al., 2022; Haas, 2008].

Of the various life course models (i.e., sensitive period; cumulative risk; recency), sensitive periods of adversity exposure best explained odds of frailty at old age for both males and females [Baranyi et al., 2022]. Childhood exposure to chronic disease and adolescent risky behaviours were found to exert direct effects on old age frailty [Farrelly, 2020],

though effects of particular sensitive periods varied by sex. Specifically, males were most susceptible to adversity during childhood; whereas females were most vulnerable during their later life in mid-adulthood [Baranyi et al., 2022]. Likewise, several studies document greater negative outcomes for males when exposed to environmental perturbations early on during gestation, whereas females experience greater risk of affective disorders when exposed to adversity during childhood [Kim et al., 2015; Sandman et al., 2013; O'Connor et al., 2002]. Ultimately, this suggests a later sensitive period for women relative to men.

Gender disparities have been largely attributed to differences in brain structure, gonadal hormones, and neuroendocrine functioning between men and women in response to stress [Bale and Epperson, 2015]. Particularly, males undergo an overall suppression of the HPA axis[3] by activational testosterone after puberty, likely contributing to a dampened stress-response effect in males at later life [Bale and Epperson, 2015]. In contrast, clinical functional magnetic resonance imaging (fMRI) analyses find fluctuations in the orbitofrontal cortex –a brain region crucial to affect determination and stress regulation– across the menstrual cycle for females in response to emotional stimuli [Amin et al., 2006; Protopopescu et al., 2005]. Potentially, this accounts partially for the disparity in sensitive periods between men and women.

In contrast to childhood factors, some studies found that socioeconomic adversity in adulthood (financial security; education; occupational status) appeared to matter more for old age frailty relative to childhood circumstances [Herr et al., 2015]. Specifically, including adulthood socioeconomic status (SES) into multivariable analyses resulted in the loss of significance for childhood deprivation in predicting old age frailty; whereas various measures of adult SES remained significant across all models [Herr et al., 2015]. But the importance of early versus later life circumstances may vary by the nature of adversity being examined. Specifically, adversity related to illness or physical harm, as investigated in the former, may exert a greater impact during earlier periods because children have minimal access to social networks or resources to cope with such stressors. Whereas socioeconomic adversities, such as financial security and occupational status, may be less relevant during childhood because children are unlikely to have a job. Hence although socioeconomic factors in childhood may be associated with greater odds of old age frailty, studies find that such effects disappear and are instead fully mediated by adulthood socioeconomic factors [Van der Linden et al., 2020]. In contrast, only childhood health (but not childhood SES and father's educational attainment) was found to be significantly related to one's trajectory of frailty in later life [Yan et al., 2022]. In decomposing the variance of the frailty index, Cao et al. [2022] similarly found that adulthood

[3]Regulation of the HPA axis comprises the coordination of brain regions to return stress response to regular baseline levels

SES (7.06%) and adulthood adversity exposures (5.70%) contributed to a much larger proportion of variance compared to childhood factors. Effects of stressors on later life frailty may therefore be heterogeneous across different 'domains' of adversities.

4.3 Recency

The recency hypothesis suggests that individuals experience a pronounced effect on their old age frailty when exposure to adversities are proximal rather than distal. Of the three life course models examined in this paper, studies found the least support for the recency model, possibly because it remains highly understudied. The only study by Marini et al. [2018] examined the sensitive period, cumulative risk, and recency models concurrently using a statistical learning approach, and found limited support for the recency hypothesis. Specifically, the recency model was only found to be salient among girls when considering their exposure to financial stress. All other forms of adversities (physical/emotional/sexual abuse; maternal psychopathy; family instability; neighbourhood disadvantage) for boys and girls were associated with a sensitive period hypothesis. No other studies have examined the recency hypothesis, ostensibly due to the relative lack of longitudinal data from childhood to adulthood.

5 Mortality Consequences of Frailty

5.1 All-cause Mortality

Frailty has been linked to a wide range of health consequences. Most frequently studied is the relationship between frailty and mortality risk. Broadly, empirical studies demonstrate that frailty is consistently associated with a greater risk of all-cause mortality. Individuals with frailty status lost up to 5.71 years of life by age 45; and 4.82 years and 4.96 years respectively for men and women by 65 years old [Hou et al., 2022]. All individual measures of frailty (walking pace; exhaustion; weight loss; physical activity; grip strength) were too associated with a shorter life expectancy, with a slow walking pace predicting the greatest loss of life (1.49 years) by age 65 [Hou et al., 2022].

Survival curves also differed significantly depending on frailty status: on average non-frail individuals experienced markedly higher 3-year survival probabilities (92.6%) compared to pre-frail (85.7%) and frail (74.2%) patients [Lee et al., 2021]. Results appear to be robust across varying operationalisations of frailty status (i.e., FRAIL scale and Rockwood's frailty index), with an elevated hazard ratio of mortality by 5.97–7.96 in 10 year follow-ups, and 3.95–6.32 in 18 year follow-ups [Salminen et al., 2020]. Meta-analysis also agreed with evidence so far, demonstrating that those with frailty status

have approximately 2.34 folds the odds of mortality [Vermeiren et al., 2016].

Such elevated risk is robustly observed across various conceptualisations of frailty, whether or not the instrument emphasises a more physical or multidimensional component of frailty [Vermeiren et al., 2016]. Dividing findings by time-to-follow-up categories produces similar results, with growing disparities in mortality risk over longer follow-up periods. Follow-up periods of 0–12 months produces the least difference in mortality risk ($OR = 1.33$), compared to lengthier follow-up periods of 12–24 months ($OR = 2.31$) and 24–60 months ($OR = 3.25$) [Vermeiren et al., 2016]. Such findings are potentially indicative of the cumulative burden conferred by frailty on individuals.

5.2 Case-specific Morality

Studies have also examined links between frailty status and cause-specific mortality. In particular, frailty is most strongly associated with respiratory illness induced mortality ($OR = 3.48$), compared to heart disease ($OR = 2.96$), cancer ($OR = 2.82$), and dementia (2.87) [Lohman et al., 2020]. Results from other studies concur with this finding, demonstrating frailty status to be highly linked with mortality induced by respiratory illnesses relative to other conditions such as strokes, cardiovascular disease, and circulatory disease [Gilmour and Ramage-Morin, 2021; Fan et al., 2020; Grabovac et al., 2019].

Few studies have however attempted elucidate the mechanisms underlying frailty and respiratory-linked mortality. Most relevant to this endeavour was the finding that healthy behaviour (here treated as multidimensional aspects of body mass and tobacco/alcohol consumption behaviours) mediated approximately 5.1% of the association between frail status and respiratory disease specific mortality. Potentially then, frailty status may impinge on the lifestyle and health choices of individuals, which produce greater respiratory disease linked mortality [Du et al., 2022]. Indeed, existing studies support such a view, finding that deaths from respiratory diseases were highly linked with smoking and drinking habits, adiposity, and sleep patterns [Murano et al., 2023].

Beyond direct associations with lifespan, frailty has also been linked to diseases comprising a core component of population mortality rates. Frailty status (and constituent frailty phenotypes) for instance predicted a hazard ratio of 1.69 and 1.91 of cardiovascular disease incidence for men and women respectively [Hou et al., 2022]. Frail individuals also tended to be more susceptible to various geriantric conditions, such as a heightened risk of malnutrition ($OR = 2.83 - 5.25$), dysmobility ($OR = 3.58 - 7.97$), disability ($OR = 2.18 - 4.46$), and having impaired cognition ($OR = 2.36 - 5.25$), compared to non-frail individuals [Lee et al., 2021]. Ultimately, evidence suggests that frailty extensively impinges on individual health across a broad range of outcomes, highlighting the urgent need to better understand its underlying mechanisms.

References

Aas, M., Bellivier, F., Bettella, F., Henry, C., Gard, S., Kahn, J.-P., Lagerberg, T. V., Aminoff, S. R., Melle, I., Leboyer, M., Jamain, S., Andreassen, O. A., and Etain, B. (2020). Childhood maltreatment and polygenic risk in bipolar disorders. *Bipolar Disorders*, 22(2):174–181.

Abbatecola, A. M. and Paolisso, G. (2008). Is There A Relationship Between Insulin Resistance and Frailty Syndrome? *Current Pharmaceutical Design*, 14(4):405–410.

Abreu, W., Tolson, D., Jackson, G. A., and Costa, N. (2020). A cross-sectional study of family caregiver burden and psychological distress linked to frailty and functional dependency of a relative with advanced dementia. *Dementia*, 19(2):301–318.

Agid, O., Shapira, B., Zislin, J., Ritsner, M., Hanin, B., Murad, H., Troudart, T., Bloch, M., Heresco-Levy, U., and Lerer, B. (1999). Environment and vulnerability to major psychiatric illness: A case control study of early parental loss in major depression, bipolar disorder and schizophrenia. *Molecular Psychiatry*, 4(2):163–172.

Aliño-Dies, M., Sánchez-Ortí, J. V., Correa-Ghisays, P., Balanzá-Martínez, V., Vila-Francés, J., Selva-Vera, G., Correa-Estrada, P., Forés-Martos, J., San-Martín Valenzuela, C., Monfort-Pañego, M., Ayesa-Arriola, R., Ruiz-Veguilla, M., Crespo-Facorro, B., and Tabarés-Seisdedos, R. (2020). Grip Strength, Neurocognition, and Social Functioning in People WithType-2 Diabetes Mellitus, Major Depressive Disorder, Bipolar Disorder, and Schizophrenia. *Frontiers in Psychology*, 11.

Alkhodary, A., Aljunid, S. M., Ismail, A., M, N. A., and S, S. (2020). The Economic Burden of Frailty among Elderly People: A Review of the Current Literature. *Malaysian Journal of Public Health Medicine*, 20(2):224–232.

Alvarado, B. E., Zunzunegui, M.-V., Béland, F., and Bamvita, J.-M. (2008). Life Course Social and Health Conditions Linked to Frailty in Latin American Older Men and Women. *The Journals of Gerontology: Series A*, 63(12):1399–1406.

Álvarez-Satta, M., Berna-Erro, A., Carrasco-Garcia, E., Alberro, A., Saenz-Antoñanzas, A., Vergara, I., Otaegui, D., and Matheu, A. (2020). Relevance of oxidative stress and inflammation in frailty based on human studies and mouse models. *Aging (Albany NY)*, 12(10):9982–9999.

Alyazidi, A. M., Shakhau, A., Huang, A., Bettwieser, S., Bender, A., and Moak, G. S. (2018). Poster Number: EI 42 - Frailty among Older Adult State Hospital Patients. *The American Journal of Geriatric Psychiatry*, 26(3, Supplement):S109–S110.

Amin, Z., Epperson, C. N., Constable, R. T., and Canli, T. (2006). Effects of estrogen variation on neural correlates of emotional response inhibition. *NeuroImage*, 32(1):457–464.

Andersen, B. B., Gundersen, H. J. G., and Pakkenberg, B. (2003). Aging of the human cerebellum: A stereological study. *Journal of Comparative Neurology*, 466(3):356–365.

Auyeung, T. W., Lee, J. S. W., Kwok, T., and Woo, J. (2011). Physical frailty predicts future cognitive decline — A four-year prospective study in 2737 cognitively normal older adults. *The Journal of nutrition, health and aging*, 15(8):690–694.

Ávila-Funes, J. A., Amieva, H., Barberger-Gateau, P., Le Goff, M., Raoux, N., Ritchie, K., Carrière, I., Tavernier, B., Tzourio, C., Gutiérrez-Robledo, L. M., and Dartigues, J.-F. (2009). Cognitive Impairment Improves the Predictive Validity of the Phenotype of Frailty for Adverse Health Outcomes: The Three-City Study. *Journal of the American Geriatrics Society*, 57(3):453–461.

Bale, T. L. and Epperson, C. N. (2015). Sex differences and stress across the lifespan. *Nature Neuroscience*, 18(10):1413–1420.

Baranyi, G., Welstead, M., Corley, J., Deary, I. J., Muniz-Terrera, G., Redmond, P., Shortt, N., Taylor, A. M., Ward Thompson, C., Cox, S. R., and Pearce, J. (2022). Association of Life-Course Neighborhood Deprivation With Frailty and Frailty Progression From Ages 70 to 82 Years in the Lothian Birth Cohort 1936. *American Journal of Epidemiology*, 191(11):1856–1866.

Barzilay, J. I., Blaum, C., Moore, T., Li Xue, Q., Hirsch, C. H., Walston, J. D., and Fried, L. P. (2007). Insulin Resistance and Inflammation as Precursors of Frailty: The Cardiovascular Health Study. *Archives of Internal Medicine*, 167(7):635–641.

Batista, F. S., Gomes, G. A. d. O., Neri, A. L., Guariento, M. E., Cintra, F. A., de Sousa, M. d. L. R., and D'Elboux, M. J. (2012). Relationship between lower-limb muscle strength and frailty among elderly people. *Sao Paulo Medical Journal*, 130:102–108.

Beckers, F., Verheyden, B., and Aubert, A. E. (2006). Aging and nonlinear heart rate control in a healthy population. *American Journal of Physiology-Heart and Circulatory Physiology*, 290(6):H2560–H2570.

Belsky, D. W., Caspi, A., Cohen, H. J., Kraus, W. E., Ramrakha, S., Poulton, R., and Moffitt, T. E. (2017). 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*, 16(4):644–651.

Blaum, C. S., Xue, Q. L., Tian, J., Semba, R. D., Fried, L. P., and Walston, J. (2009). Is Hyperglycemia Associated with Frailty Status in Older Women? *Journal of the American Geriatrics Society*, 57(5):840–847.

Bollheimer, L. C., Buettner, R., Pongratz, G., Brunner-Ploss, R., Hechtl, C., Banas, M., Singler, K., Hamer, O. W., Stroszczynski, C., Sieber, C. C., and Fellner, C. (2012). Sarcopenia in the aging high-fat fed rat: A pilot study for modeling sarcopenic obesity in rodents. *Biogerontology*, 13(6):609–620.

Borges, M. K., Canevelli, M., Cesari, M., and Aprahamian, I. (2019). Frailty as a Predictor of Cognitive Disorders: A Systematic Review and Meta-Analysis. *Frontiers in Medicine*, 6.

Bornscheuer, L., Gauffin, K., and Almquist, Y. B. (2024). Mapping resilience: A scoping review on mediators and moderators of childhood adversity with a focus on gender patterns. *BMJ Open*, 14(9):e080259.

Bouillon, K., Kivimaki, M., Hamer, M., Sabia, S., Fransson, E. I., Singh-Manoux, A., Gale, C. R., and Batty, G. D. (2013). Measures of frailty in population-based studies: An overview. *BMC Geriatrics*, 13(1):64.

Bourg, P., Salottolo, K., Klein, J., and Bar-Or, D. (2021). Can a biomarker for oxidative stress and antioxidant reserves identify frailty in geriatric trauma patients? *Injury*, 52(10):2908–2913.

Boyes, M. E., Hasking, P. A., and Martin, G. (2016). Adverse Life Experience and Psychological Distress in Adolescence: Moderating and Mediating Effects of Emotion Regulation and Rumination. *Stress and Health*, 32(4):402–410.

Cameron, K. A., Song, J., Manheim, L. M., and Dunlop, D. D. (2010). Gender Disparities in Health and Healthcare Use Among Older Adults. *Journal of Women's Health*, 19(9):1643–1650.

Cao, X., Ma, C., Zheng, Z., He, L., Hao, M., Chen, X., Crimmins, E. M., Gill, T. M., Levine, M. E., and Liu, Z. (2022). Contribution of life course circumstances to the acceleration of phenotypic and functional aging: A retrospective study. *eClinicalMedicine*, 51.

Cardoso, A. L., Fernandes, A., Aguilar-Pimentel, J. A., de Angelis, M. H., Guedes, J. R., Brito, M. A., Ortolano, S., Pani, G., Athanasopoulou, S., Gonos, E. S., Schosserer, M., Grillari, J., Peterson, P., Tuna, B. G., Dogan, S., Meyer, A., van Os, R., and Trendelenburg, A.-U. (2018). Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases. *Ageing Research Reviews*, 47:214–277.

Carpenter, L. L., Tyrka, A. R., Ross, N. S., Khoury, L., Anderson, G. M., and Price, L. H. (2009). Effect of Childhood Emotional Abuse and Age on Cortisol Responsivity in Adulthood. *Biological psychiatry*, 66(1):69–75.

Cawthon, P. M., Ensrud, K. E., Laughlin, G. A., Cauley, J. A., Dam, T.-T. L., Barrett-Connor, E., Fink, H. A., Hoffman, A. R., Lau, E., Lane, N. E., Stefanick, M. L., Cummings, S. R., Orwoll, E. S., and for the Osteoporotic Fractures in Men (MrOS) Research Group (2009). Sex Hormones and Frailty in Older Men: The Osteoporotic Fractures in Men (MrOS) Study. *The Journal of Clinical Endocrinology & Metabolism*, 94(10):3806–3815.

Cesari, M., Landi, F., Vellas, B., Bernabei, R., and Marzetti, E. (2014). Sarcopenia and Physical Frailty: Two Sides of the Same Coin. *Frontiers in Aging Neuroscience*, 6.

Cesari, M., Leeuwenburgh, C., Lauretani, F., Onder, G., Bandinelli, S., Maraldi, C., Guralnik, J. M., Pahor, M., and Ferrucci, L. (2006). Frailty syndrome and skeletal muscle: Results from the Invecchiare in Chianti study2. *The American Journal of Clinical Nutrition*, 83(5):1142–1148.

Chaves, P. H. M., Varadhan, R., Lipsitz, L. A., Stein, P. K., Windham, B. G., Tian, J., Fleisher, L. A., Guralnik, J. M., and Fried, L. P. (2008). Physiological Complexity Underlying Heart Rate Dynamics and Frailty Status in Community-Dwelling Older Women. *Journal of the American Geriatrics Society*, 56(9):1698–1703.

Chen, X., Mao, G., and Leng, S. X. (2014). Frailty syndrome: An overview. *Clinical Interventions in Aging*, 9:433–441.

Coburn, D. (2004). Beyond the income inequality hypothesis: Class, neo-liberalism, and health inequalities. *Social Science & Medicine*, 58(1):41–56.

Cruz-Jentoft, A. J., Baeyens, J. P., Bauer, J. M., Boirie, Y., Cederholm, T., Landi, F., Martin, F. C., Michel, J.-P., Rolland, Y., Schneider, S. M., Topinková, E., Vandewoude, M., and Zamboni, M. (2010). Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age and Ageing*, 39(4):412–423.

Cruz-Jentoft, A. J., Kiesswetter, E., Drey, M., and Sieber, C. C. (2017). Nutrition, frailty, and sarcopenia. *Aging Clinical and Experimental Research*, 29(1):43–48.

Davies, B., García, F., Ara, I., Artalejo, F. R., Rodriguez-Mañas, L., and Walter, S. (2018). Relationship Between Sarcopenia and Frailty in the Toledo Study of Healthy Aging: A Population Based Cross-Sectional Study. *Journal of the American Medical Directors Association*, 19(4):282–286.

de Labra, C., Guimaraes-Pinheiro, C., Maseda, A., Lorenzo, T., and Millán-Calenti, J. C. (2015). Effects of physical exercise interventions in frail older adults: A systematic review of randomized controlled trials. *BMC Geriatrics*, 15(1):1–16.

Dimitriadis, M. M., Jeuring, H. W., Marijnissen, R. M., Wieringa, T. H., Hoogendijk, E. O., and Oude Voshaar, R. C. (2023). Adverse Childhood Experiences and frailty in later life: A prospective population-based cohort study. *Age and Ageing*, 52(2):afad010.

Ding, X., Barban, N., and Mills, M. C. (2019). Educational attainment and allostatic load in later life: Evidence using genetic markers. *Preventive Medicine*, 129:105866.

Dowd, J. B., Simanek, A. M., and Aiello, A. E. (2009). Socio-economic status, cortisol and allostatic load: A review of the literature. *International Journal of Epidemiology*, 38(5):1297–1309.

Dowd, J. B., Simanek, A. M., and Aiello, A. E. (2024). (PDF) Socio-Economic Status, Cortisol and Allostatic Load: A Review of the Literature. *International Journal of Epidemiology*, 38(5):1297–1309.

Du, M., Tao, L., Liu, M., and Liu, J. (2022). Mediation of Healthy Behaviour on the Association of Frailty with Respiratory Diseases Mortality among 0.4 Million Participants: A Prospective Cohort Study from UK Biobank. *Nutrients*, 14(23):5046.

Dunn, E. C., Soare, T. W., Zhu, Y., Simpkin, A. J., Suderman, M. J., Klengel, T., Smith, A. D. A. C., Ressler, K. J., and Relton, C. L. (2019). Sensitive Periods for the Effect of Childhood Adversity on DNA Methylation: Results From a Prospective, Longitudinal Study. *Biological Psychiatry*, 85(10):838–849.

Fan, J., Yu, C., Guo, Y., Bian, Z., Sun, Z., Yang, L., Chen, Y., Du, H., Li, Z., Lei, Y., Sun, D., Clarke, R., Chen, J., Chen, Z., Lv, J., and Li, L. (2020). Frailty index and all-cause and cause-specific mortality in Chinese adults: A prospective cohort study. *The Lancet Public Health*, 5(12):e650–e660.

Farrelly, M. M. (2020). *Life Course Origins of Frailty in Later Life*. Thesis, Purdue University Graduate School.

Farrow, M., Biglands, J., Tanner, S. F., Clegg, A., Brown, L., Hensor, E. M. A., O'Connor, P., Emery, P., and Tan, A. L. (2021). The effect of ageing on skeletal muscle as assessed by quantitative MR imaging: An association with frailty and muscle strength. *Aging Clinical and Experimental Research*, 33(2):291–301.

Forti, P., Maioli, F., Lega, M. V., Montanari, L., Coraini, F., and Zoli, M. (2014). Combination of the Clock Drawing Test with the Physical Phenotype of Frailty for the Prediction of Mortality and Other Adverse Outcomes in Older Community Dwellers without Dementia. *Gerontology*, 60(3):204–211.

Forti, P., Rietti, E., Pisacane, N., Olivelli, V., Maltoni, B., and Ravaglia, G. (2012). A comparison of frailty indexes for prediction of adverse health outcomes in an elderly cohort. *Archives of Gerontology and Geriatrics*, 54(1):16–20.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W. J., Burke, G., McBurnie, M. A., and Cardiovascular Health Study Collaborative Research Group (2001). Frailty in older adults: Evidence for a phenotype. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 56(3):M146–156.

Gao, T., Han, S., Mo, G., Sun, Q., Zhang, M., and Liu, H. (2022). A positive association between hunger in childhood and frailty in old age: Findings from the Chinese longitudinal healthy longevity survey. *Frontiers in Medicine*, 9.

Gerozissis, K. (2010). The Brain-insulin connection, metabolic diseases and related pathologies. In *Diabetes, Insulin and Alzheimer's Disease*, pages 21–42. Springer-Verlag, Berlin, Heidelberg.

Gilmour, H. and Ramage-Morin, P. L. (2021). Association of frailty and pre-frailty with increased risk of mortality among older Canadians. *Health Reports*, 32(4):15–26.

Grabovac, I., Haider, S., Mogg, C., Majewska, B., Drgac, D., Oberndorfer, M., and Dorner, T. E. (2019). Frailty Status Predicts All-Cause and Cause-Specific Mortality in Community Dwelling Older Adults. *Journal of the American Medical Directors Association*, 20(10):1230–1235.e2.

Gruenewald, T. L., Seeman, T. E., Karlamangla, A. S., and Sarkisian, C. A. (2009). Allostatic Load and Frailty in Older Adults. *Journal of the American Geriatrics Society*, 57(9):1525–1531.

Haapanen, M. J., Perälä, M. M., Salonen, M. K., Kajantie, E., Simonen, M., Pohjolainen, P., Pesonen, A. K., Räikkönen, K., Eriksson, J. G., and von Bonsdorff, M. B. (2018). Early life stress and frailty in old age: The Helsinki birth cohort study. *BMC Geriatrics*, 18(1):1–8.

Haas, S. (2008). Trajectories of functional health: The 'long arm' of childhood health and socioeconomic factors. *Social Science & Medicine*, 66(4):849–861.

Han, E. S., Lee, Y., and Kim, J. (2014). Association of cognitive impairment with frailty in community-dwelling older adults. *International Psychogeriatrics*, 26(1):155–163.

Hayward, M. D. and Gorman, B. K. (2004). The long arm of childhood: The influence of early-life social conditions on men's mortality. *Demography*, 41(1):87–107.

Herd, P., Robert, S. A., and House, J. S. (2011). Chapter 9 - Health Disparities Among Older Adults: Life Course Influences and Policy Solutions. In Binstock, R. H. and George, L. K., editors, *Handbook of Aging and the Social Sciences (Seventh Edition)*, Handbooks of Aging, pages 121–134. Academic Press, San Diego.

Herr, M., Robine, J.-M., Aegerter, P., Arvieu, J.-J., and Ankri, J. (2015). Contribution of socioeconomic position over life to frailty differences in old age: Comparison of life-course models in a French sample of 2350 old people. *Annals of Epidemiology*, 25(9):674–680.e1.

Hirani, V., Naganathan, V., Blyth, F., Le Couteur, D. G., Seibel, M. J., Waite, L. M., Handelsman, D. J., and Cumming, R. G. (2017). Longitudinal associations between body composition, sarcopenic obesity and outcomes of frailty, disability, institutionalisation and mortality in community-dwelling older men: The Concord Health and Ageing in Men Project. *Age and Ageing*, 46(3):413–420.

Hirata, Y., Yamamoto, E., Tokitsu, T., Kusaka, H., Fujisue, K., Kurokawa, H., Sugamura, K., Maeda, H., Tsujita, K., Kaikita, K., Hokimoto, S., Sugiyama, S., and Ogawa, H. (2015). Reactive Oxygen Metabolites are Closely Associated With the Diagnosis and Prognosis of Coronary Artery Disease. *Journal of the American Heart Association*, 4(2):e001451.

Homan, P. (2019). Structural Sexism and Health in the United States: A New Perspective on Health Inequality and the Gender System. *American Sociological Review*, 84(3):486–516.

Hou, Y., Xu, C., Lu, Q., Zhang, Y., Cao, Z., Li, S., Yang, H., Sun, L., Cao, X., Zhao, Y., and Wang, Y. (2022). Associations of frailty with cardiovascular disease and life expectancy: A prospective cohort study. *Archives of Gerontology and Geriatrics*, 99:104598.

Howard, C., Ferrucci, L., Sun, K., Fried, L. P., Walston, J., Varadhan, R., Guralnik, J. M., and Semba, R. D. (2007). Oxidative protein damage is associated with poor grip strength among older women living in the community. *Journal of Applied Physiology*, 103(1):17–20.

Inglés, M., Gambini, J., Carnicero, J. A., García-García, F. J., Rodríguez-Mañas, L., Olaso-González, G., Dromant, M., Borrás, C., and Viña, J. (2014). Oxidative Stress Is Related to Frailty, Not to Age or Sex, in a Geriatric Population: Lipid and Protein Oxidation as Biomarkers of Frailty. *Journal of the American Geriatrics Society*, 62(7):1324–1328.

Isakjee, A. (2017). Welfare State Regimes: A Literature Review. In *IRIS Working Paper Series*, University of Birmingham. Institute for Research into Superdiversity.

Juwita, H. R., Roemintoyo, and Usodo, B. (2020). The Role of Adversity Quotient in the Field of Education: A Review of the Literature on Educational Development. *International Journal of Educational Methodology*, 6(3):507–515.

Ke, Z., Wen, H., Huang, R., Xu, X., Yang, K., Liu, W., Wang, S., Zhang, X., Guo, Y., Liao, X., Zhuang, X., Zhao, J., Pan, L., and Liao, L. (2024). Long-term insulin resistance is associated with frailty, frailty progression, and cardiovascular disease. *Journal of Cachexia, Sarcopenia and Muscle*, 15(4):1578–1586.

Khansari, N., Shakiba, Y., and Mahmoudi, M. (2009). Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer. *Recent Patents on Inflammation & Allergy Drug Discovery*, 3(1):73–80.

Kim, D. R., Bale, T. L., and Epperson, C. N. (2015). Prenatal Programming of Mental Illness: Current Understanding of Relationship and Mechanisms. *Current Psychiatry Reports*, 17(2):1–9.

Knudsen, E. I. (2004). Sensitive Periods in the Development of the Brain and Behavior. *Journal of Cognitive Neuroscience*, 16(8):1412–1425.

Kuhlmann, E. and Annandale, E. (2015). Gender and Healthcare Policy. In *The Palgrave International Handbook of Healthcare Policy and Governance*, pages 578–596. Palgrave Macmillan, London.

Laskou, F., Fuggle, N. R., Patel, H. P., Jameson, K., Cooper, C., and Dennison, E. (2022). Associations of osteoporosis and sarcopenia with frailty and multimorbidity among participants of the Hertfordshire Cohort Study. *Journal of Cachexia, Sarcopenia and Muscle*, 13(1):220–229.

Laudisio, A., Navarini, L., Margiotta, D. P. E., Fontana, D. O., Chiarella, I., Spitaleri, D., Bandinelli, S., Gemma, A., Ferrucci, L., and Incalzi, R. A. (2019). The Association of Olfactory Dysfunction, Frailty, and Mortality Is Mediated by Inflammation: Results from the InCHIANTI Study. *Journal of Immunology Research*, 2019(1):3128231.

Lee, H., Chong, J., Jung, H.-W., Baek, J. Y., Lee, E., and Jang, I.-Y. (2021). Association of the FRAIL Scale with Geriatric Syndromes and Health-Related Outcomes in Korean Older Adults. *Annals of Geriatric Medicine and Research*, 25(2):79–85.

Leeuwenburgh, C. (2003). Role of Apoptosis in Sarcopenia. *The Journals of Gerontology: Series A*, 58(11):M999–M1001.

Leng, S., Chaves, P., Koenig, K., and Walston, J. (2002). Serum Interleukin-6 and Hemoglobin as Physiological Correlates in the Geriatric Syndrome of Frailty: A Pilot Study. *Journal of the American Geriatrics Society*, 50(7):1268–1271.

Lipsitz, L. A. (2004). Physiological Complexity, Aging, and the Path to Frailty. *Science of Aging Knowledge Environment*, 2004(16):pe16–pe16.

Liu, C. K., Lyass, A., Larson, M. G., Massaro, J. M., Wang, N., D'Agostino, R. B., Benjamin, E. J., and Murabito, J. M. (2016). Biomarkers of oxidative stress are associated with frailty: The Framingham Offspring Study. *Age*, 38(1):1.

Lohman, M. C., Sonnega, A. J., Resciniti, N. V., and Leggett, A. N. (2020). Frailty Phenotype and Cause-Specific Mortality in the United States. *The Journals of Gerontology: Series A*, 75(10):1935–1942.

Lorenzo-López, L., López-López, R., Maseda, A., Buján, A., Rodríguez-Villamil, J. L., and Millán-Calenti, J. C. (2019). Changes in frailty status in a community-dwelling cohort of older adults: The VERISAÚDE study. *Maturitas*, 119:54–60.

Mäkikallio, A. M., Mäkikallio, T. H., Korpelainen, J. T., Sotaniemi, K. A., Huikuri, H. V., and Myllylä, V. V. (2004). Heart rate dynamics predict poststroke mortality. *Neurology*, 62(10):1822–1826.

Marini, S., Davis, K. A., Soare, T. W., Suderman, M. J., Simpkin, A. J., Smith, A. D., Wolf, E. J., Relton, C. L., and Dunn, E. C. (2018). Predicting cellular aging following exposure to adversity: Does accumulation, recency, or developmental timing of exposure matter?

Mauk, K. L. (2017). *Gerontological Nursing Competencies for Care*. Jones & Bartlett Learning.

Mian, O., Anderson, L. N., Belsky, D. W., Gonzalez, A., Ma, J., Sloboda, D. M., Bowdish, D. M., and Verschoor, C. P. (2021). Associations of Adverse Childhood Experiences with Frailty in Older Adults: A Cross-Sectional Analysis of Data from the Canadian Longitudinal Study on Aging. *Gerontology*, 68(10):1091–1100.

Mitnitski, A. B., Mogilner, A. J., and Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *TheScientificWorldJournal*, 1:323–336.

Mohr, B. A., Bhasin, S., Kupelian, V., Araujo, A. B., O'Donnell, A. B., and McKinlay, J. B. (2007). Testosterone, Sex Hormone–Binding Globulin, and Frailty in Older Men. *Journal of the American Geriatrics Society*, 55(4):548–555.

Mone, P., Gennaro, S. D., Frullone, S., Marro, A., and Santulli, G. (2023). Hyperglycemia drives the transition from pre-frailty to frailty: The Monteforte study. *European Journal of Internal Medicine*, 111:135–137.

Murano, H., Inoue, S., Sato, K., Sato, M., Igarashi, A., Fujimoto, S., Iseki, K., Moriyama, T., Shibagaki, Y., Kasahara, M., Narita, I., Yamagata, K., Tsuruya, K., Kondo, M., Asahi, K., Watanabe, T., Konta, T., and Watanabe, M. (2023). The effect of lifestyle on the mortality associated with respiratory diseases in the general population. *Scientific Reports*, 13(1):8272.

Namioka, N., Hanyu, H., Hirose, D., Hatanaka, H., Sato, T., and Shimizu, S. (2017). Oxidative stress and inflammation are associated with physical frailty in patients with Alzheimer's disease. *Geriatrics & Gerontology International*, 17(6):913–918.

Nascimento, C. M., Ingles, M., Salvador-Pascual, A., Cominetti, M. R., Gomez-Cabrera, M. C., and Viña, J. (2019). Sarcopenia, frailty and their prevention by exercise. *Free Radical Biology and Medicine*, 132:42–49.

Ng, T. P., Feng, L., Nyunt, M. S. Z., Larbi, A., and Yap, K. B. (2014). Frailty in Older Persons: Multisystem Risk Factors and the Frailty Risk Index (FRI). *Journal of the American Medical Directors Association*, 15(9):635–642.

O'Caoimh, R., Sezgin, D., O'Donovan, M. R., Molloy, D. W., Clegg, A., Rockwood, K., and Liew, A. (2021). Prevalence of frailty in 62 countries across the world: A systematic review and meta-analysis of population-level studies. *Age and Ageing*, 50(1):96–104.

O'Connor, T. G., Heron, J., Golding, J., Beveridge, M., and Glover, V. (2002). Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years: Report from the Avon Longitudinal Study of Parents and Children. *The British Journal of Psychiatry*, 180(6):502–508.

Ozkok, S., Aydin, C. O., Sacar, D. E., Catikkas, N. M., Erdogan, T., Bozkurt, M. E., Kilic, C., Karan, M. A., and Bahat, G. (2022). Sarcopenic obesity versus sarcopenia alone with the use of probable sarcopenia definition for sarcopenia: Associations with frailty and physical performance. *Clinical Nutrition*, 41(11):2509–2516.

Pakpahan, E., Hoffmann, R., and Kröger, H. (2017). The long arm of childhood circumstances on health in old age: Evidence from SHARELIFE. *Advances in Life Course Research*, 31:1–10.

Pearson, E., Siskind, D., Hubbard, R. E., Gordon, E. H., Coulson, E. J., and Warren, N. (2022). Frailty and severe mental illness: A systematic review and narrative synthesis. *Journal of Psychiatric Research*, 147:166–175.

Pérez-Tasigchana, R. F., León-Muñoz, L. M., Lopez-Garcia, E., Gutierrez-Fisac, J. L., Laclaustra, M., Rodríguez-Artalejo, F., and Guallar-Castillón, P. (2017). Metabolic syndrome and insulin resistance are associated with frailty in older adults: A prospective cohort study. *Age and Ageing*, 46(5):807–812.

Polidori, M. C. and Mecocci, P. (2022). Modeling the dynamics of energy imbalance: The free radical theory of aging and frailty revisited. *Free Radical Biology and Medicine*, 181:235–240.

Protopopescu, X., Pan, H., Altemus, M., Tuescher, O., Polanecsky, M., McEwen, B., Silbersweig, D., and Stern, E. (2005). Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle. *Proceedings of the National Academy of Sciences*, 102(44):16060–16065.

Reiner, A. P., Aragaki, A. K., Gray, S. L., Wactawski-Wende, J., Cauley, J. A., Cochrane, B. B., Kooperberg, C. L., Woods, N. F., and LaCroix, A. Z. (2009). Inflammation and Thrombosis Biomarkers and Incident Frailty in Postmenopausal Women. *The American Journal of Medicine*, 122(10):947–954.

Richards, M. and Wadsworth, M. E. J. (2004). Long term effects of early adversity on cognitive function. *Archives of Disease in Childhood*, 89(10):922–927.

Rockwood, K., Andrew, M., and Mitnitski, A. (2007). A comparison of two approaches to measuring frailty in elderly people. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 62(7):738–743.

Rockwood, K. and Mitnitski, A. (2012). How might deficit accumulation give rise to frailty? *Journal of Frailty & Aging*, pages 1–4.

Salminen, M., Viljanen, A., Eloranta, S., Viikari, P., Wuorela, M., Vahlberg, T., Isoaho, R., Kivelä, S.-L., Korhonen, P., Irjala, K., Löppönen, M., and Viikari, L. (2020). Frailty and mortality: An 18-year follow-up study among Finnish community-dwelling older people. *Aging Clinical and Experimental Research*, 32(10):2013–2019.

Sandman, C. A., Glynn, L. M., and Davis, E. P. (2013). Is there a viability–vulnerability tradeoff? Sex differences in fetal programming. *Journal of Psychosomatic Research*, 75(4):327–335.

Sargent, L., Nalls, M., Starkweather, A., Hobgood, S., Thompson, H., Amella, E. J., and Singleton, A. (2018). Shared biological pathways for frailty and cognitive impairment: A systematic review. *Ageing Research Reviews*, 47:149–158.

Saum, K.-U., Dieffenbach, A. K., Jansen, E. H., Schöttker, B., Holleczek, B., Hauer, K., and Brenner, H. (2015). Association between Oxidative Stress and Frailty in an Elderly German Population: Results from the ESTHER Cohort Study. *Gerontology*, 61(5):407–415.

Schaap, L. A., Pluijm, S. M. F., Deeg, D. J. H., Harris, T. B., Kritchevsky, S. B., Newman, A. B., Colbert, L. H., Pahor, M., Rubin, S. M., Tylavsky, F. A., Visser, M., and for the Health ABC Study (2009). Higher Inflammatory Marker Levels in Older Persons: Associations With 5-Year Change in Muscle Mass and Muscle Strength. *The Journals of Gerontology: Series A*, 64A(11):1183–1189.

Schmahl, O. C., Jeuring, H. W., Aprahamian, I., Naarding, P., Marijnissen, R. M., Hendriks, G. J., Fluiter, M., Rhebergen, D., Lugtenburg, A., Lammers, M. W., van den Brink, R. H. S., and Oude Voshaar, R. C. (2021). Impact of childhood trauma on multidimensional frailty in older patients with a unipolar depressive-, anxiety- or somatic symptom disorder. *Archives of Gerontology and Geriatrics*, 96:104452.

Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M., and Rockwood, K. (2008). A standard procedure for creating a frailty index. *BMC Geriatrics*, 8(1):24.

Semba, R. D., Ferrucci, L., Sun, K., Walston, J., Varadhan, R., Guralnik, J. M., and Fried, L. P. (2007). Oxidative Stress and Severe Walking Disability among Older Women. *The American Journal of Medicine*, 120(12):1084–1089.

Sheridan, M. A. and McLaughlin, K. A. (2016). Neurobiological models of the impact of adversity on education. *Current Opinion in Behavioral Sciences*, 10:108–113.

Somekawa, S., Mine, T., Ono, K., Hayashi, N., Obuchi, S., Yoshida, H., Kawai, H., Fujiwara, Y., Hirano, H., Kojima, M., Ihara, K., and Kim, H. (2017). Relationship between sensory perception and frailty in a community-dwelling elderly population. *The Journal of nutrition, health and aging*, 21(6):710–714.

Soysal, P., Stubbs, B., Lucato, P., Luchini, C., Solmi, M., Peluso, R., Sergi, G., Isik, A. T., Manzato, E., Maggi, S., Maggio, M., Prina, A. M., Cosco, T. D., Wu, Y.-T., and Veronese, N. (2016). Inflammation and frailty in the elderly: A systematic review and meta-analysis. *Ageing Research Reviews*, 31:1–8.

Stenroth, S. M., Pynnönen, K., Haapanen, M. J., Vuoskoski, P., Mikkola, T. M., Eriksson, J. G., and von Bonsdorff, M. B. (2023). Association between resilience and frailty in older age: Findings from the Helsinki Birth Cohort Study. *Archives of Gerontology and Geriatrics*, 115:105119.

Swiecicka, A., Lunt, M., Ahern, T., O'Neill, T. W., Bartfai, G., Casanueva, F. F., Forti, G., Giwercman, A., Han, T. S., Lean, M. E. J., Pendleton, N., Punab, M., Slowikowska-Hilczer, J., Vanderschueren, D., Huhtaniemi, I. T., Wu, F. C. W., Rutter, M. K., and for the EMAS Study Group (2017). Nonandrogenic Anabolic Hormones Predict Risk of Frailty: European Male Ageing Study Prospective Data. *The Journal of Clinical Endocrinology & Metabolism*, 102(8):2798–2806.

Syslová, K., Böhmová, A., Mikoška, M., Kuzma, M., Pelclová, D., and Kačer, P. (2014). Multimarker Screening of Oxidative Stress in Aging. *Oxidative Medicine and Cellular Longevity*, 2014:562860.

Szanton, S., Allen, J., Seplaki, C., Bandeen-Roche, K., and Fried, L. (2009). Allostatic Load and Frailty in the Women's Health and Aging Studies. *Biological Research For Nursing*, 10(3):248–256.

Tajar, A., Lee, D. M., Pye, S. R., O'Connell, M. D. L., Ravindrarajah, R., Gielen, E., Boonen, S., Vanderschueren, D., Pendleton, N., Finn, J. D., Bartfai, G., Casanueva, F. F., Forti, G., Giwercman, A., Han, T. S., Huhtaniemi, I. T., Kula, K., Lean, M. E. J., Punab, M., Wu, F. C. W., and O'Neill, T. W. (2013). The association of frailty with serum 25-hydroxyvitamin D and parathyroid hormone levels in older European men. *Age and Ageing*, 42(3):352–359.

Tan, B. K. J., Man, R. E. K., Gan, A. T. L., Fenwick, E. K., Varadaraj, V., Swenor, B. K., Gupta, P., Wong, T. Y., Trevisan, C., Lorenzo-López, L., Maseda, A., Millán-Calenti, J. C., Schwanke, C. H. A., Liljas, A., Al Snih, S., Tokuda, Y., and Lamoureux, E. L. (2020). Is Sensory Loss an Understudied Risk Factor for Frailty? A Systematic Review and Meta-analysis. *The Journals of Gerontology: Series A*, 75(12):2461–2470.

Tao, Y., Wang, H., Luo, J., Zhang, H., Zhang, W., Yu, M., Ji, S., Peng, S., and Zhang, X. (2024). The Association between Adverse Childhood Experiences and Frailty: A Systematic Review. *Journal of the American Medical Directors Association*, 25(7):105042.

Tsang, R. S. M., Gallacher, J. E., and Bauermeister, S. (2022). The long arm of childhood socioeconomic deprivation on mid- to later-life cognitive trajectories: A cross-cohort analysis. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 14(1):e12322.

Van der Linden, B. W. A., Cheval, B., Sieber, S., Orsholits, D., Guessous, I., Stringhini, S., Gabriel, R., Aartsen, M., Blane, D., Courvoisier, D., Burton-Jeangros, C., Kliegel, M., and Cullati, S. (2020). Life Course Socioeconomic Conditions and Frailty at Older Ages. *The Journals of Gerontology: Series B*, 75(6):1348–1357.

Van Der Linden, B. W. A., Sieber, S., Cheval, B., Orsholits, D., Guessous, I., Gabriel, R., Von Arx, M., Kelly-Irving, M., Aartsen, M., Blane, D., Boisgontier, M. P., Courvoisier, D., Oris, M., Kliegel, M., and Cullati, S. (2020). Life-Course Circumstances and Frailty in Old Age Within Different European Welfare Regimes: A Longitudinal Study With SHARE. *The Journals of Gerontology: Series B*, 75(6):1326–1335.

Varma, V. R., Hausdorff, J. M., Studenski, S. A., Rosano, C., Camicioli, R., Alexander, N. B., Chen, W. G., Lipsitz, L. A., and Carlson, M. C. (2016). Aging, the Central Nervous System, and Mobility in Older Adults: Interventions. *The Journals of Gerontology: Series A*, 71(11):1451–1458.

Vermeiren, S., Vella-Azzopardi, R., Beckwée, D., Habbig, A.-K., Scafoglieri, A., Jansen, B., Bautmans, I., Bautmans, I., Verté, D., Beyer, I., Petrovic, M., De Donder, L., Kardol, T., Rossi, G., Clarys, P., Scafoglieri, A., Cattrysse, E., de Hert, P., and Jansen, B. (2016). Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. *Journal of the American Medical Directors Association*, 17(12):1163.e1–1163.e17.

Viña, J., Rodriguez-Mañas, L., Salvador-Pascual, A., Tarazona-Santabalbina, F. J., and Gomez-Cabrera, M. C. (2016). Exercise: The lifelong supplement for healthy ageing and slowing down the onset of frailty. *The Journal of Physiology*, 594(8):1989–1999.

Volkert, D. (2011). The role of nutrition in the prevention of sarcopenia. *Wiener medizinische Wochenschrift (1946)*, 161(17-18):409–415.

Wade, M., Wright, L., and Finegold, K. E. (2022). The effects of early life adversity on children's mental health and cognitive functioning. *Translational Psychiatry*, 12(1):1–12.

Wallace, W. H. B. and Kelsey, T. W. (2010). Human Ovarian Reserve from Conception to the Menopause. *PLOS ONE*, 5(1):e8772.

Walston, J. (2004). Frailty - The Search For Underlying Causes. *Science of Aging Knowledge Environment*, 2004(4):pe4–pe4.

Wang, Q. (2023a). Gender-specific association of adverse childhood experiences with frailty index level and trajectory in China. *Maturitas*, 170:1–8.

Wang, Q. (2023b). Social contexts and cross-national differences in association between adverse childhood experiences and frailty index. *SSM - Population Health*, 22:101408.

Woo, J., Leung, J., and Morley, J. E. (2012). Comparison of Frailty Indicators Based on Clinical Phenotype and the Multiple Deficit Approach in Predicting Mortality and Physical Limitation. *Journal of the American Geriatrics Society*, 60(8):1478–1486.

Wu, I.-C., Shiesh, S.-C., Kuo, P.-H., and Lin, X.-Z. (2009). High Oxidative Stress Is Correlated with Frailty in Elderly Chinese. *Journal of the American Geriatrics Society*, 57(9):1666–1671.

Yan, Y., Cai, L., and Lu, N. (2022). Childhood experiences and frailty trajectory among middle-aged and older adults in China. *European Journal of Ageing*, 19(4):1601–1615.

Yang, G., Cao, X., Yu, J., Li, X., Zhang, L., Zhang, J., Ma, C., Zhang, N., Lu, Q., Wu, C., Chen, X., Hoogendijk, E. O., Gill, T. M., and Liu, Z. (2024). Association of Childhood Adversity With Frailty and the Mediating Role of Unhealthy Lifestyle: A Lifespan Analysis. *The American Journal of Geriatric Psychiatry*, 32(1):71–82.

Yeap, B. B., Paul Chubb, S. A., Lopez, D., Ho, K. K. Y., Hankey, G. J., and Flicker, L. (2013). Associations of insulin-like growth factor-I and its binding proteins and testosterone with frailty in older men. *Clinical Endocrinology*, 78(5):752–759.

Zaslavsky, O., Cochrane, B. B., Thompson, H. J., Woods, N. F., Herting, J. R., and LaCroix, A. (2012). Frailty: A Review of the First Decade of Research. *Biological Research For Nursing*.

Zhang, J., Xu, L., Sun, L., Li, J., and Qin, W. (2020). Gender difference in the association of frailty and health care utilization among Chinese older adults: Results from a population-based study. *Aging Clinical and Experimental Research*, 32(10):1985–1991.