High-Risk Medication Use, Frailty and Hospitalization among Older Assisted Living Residents

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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ABSTRACT

Background: With substantial comorbidity, high levels of medication use and age-related physiological changes, older adults are at an increased risk of drug-related errors and adverse events. Of particular concern are (i) antipsychotic medications, which are often prescribed off-label to individuals with dementia; and (ii) high-risk (HR) drugs (anticoagulants, oral antiplatelet agents, insulins, and oral hypoglycemic agents), which have been shown to be responsible for the majority of drug-related hospital admissions. Given the risk associated with these medications, medication management and monitoring are particularly important for older individuals at risk of adverse drug events. However, assisted living (AL) facilities, increasingly popular residential options for older adults requiring supportive care, are often characterized by lower levels of staffing and professional service, raising concerns about the care and oversight of vulnerable older adults in these settings. The concept of frailty offers a promising avenue for identifying vulnerable older adults who may require increased monitoring when using high-risk medications; however, frailty has been relatively unexplored in this context or setting.

Objectives: The present research addresses knowledge gaps with respect to frailty and medication use by: (i) estimating the baseline prevalence of HR (anticoagulants, oral antiplatelet agents, insulins, and oral hypoglycemic agents) /antipsychotic medication use and frailty among AL residents using the frailty index (FI), cardiovascular health study (CHS) criteria, and health instability (CHESS) scale (ii) examining the associations of high-risk / antipsychotic medication use and selected frailty measures with risk of inpatient hospitalization over 1 year; and, (iii) examine the role of these 3 frailty measures in modifying the association between high-risk/antipsychotic medication exposure and hospitalization risk over 1 year.

Methods: 1,089 residents of 59 Assisted Living (AL) facilities from the Alberta Continuing Care Epidemiological Studies (ACCES) were included as participants (mean age 84.9±7.3; 77% female). Baseline (2006-08) and 1-year follow-up assessments of resident clinical and drug use data were carried out by research nurses using the interRAI-AL. Facility-level data was captured through administrator interviews. Hospitalization events were captured through linkage with provincial health service utilization data from the Alberta Inpatient Discharge Abstract Database. Multivariable Cox proportional hazards models were used to estimate risk of hospitalization associated with frailty, medication exposure, and medication -frailty interaction terms.

Results: Among AL residents, the prevalence of pre-frail/frail residents was 38.9%/27.5% for the FI; 55.0%/19.2% for the CHS; and, 29.4%/24.4% for the CHESS scale. The cumulative annual incidence of hospitalization was 38.9% (35.9-41.9%). All 3 frailty measures were significantly associated with hospitalization after adjusting for age, sex and comorbidity, with the highest risk observed for frail (vs. non-frail) residents defined by the CHS criteria (adj. HR=2.11, 95% CI 1.53-2.92). Overall, use of antipsychotics (26.4% [94.0% atypical agents]), and use of any of the specified HR medication classes (63.5% using at least 1 HR medication class) showed no association with hospitalization. However, the FI, and occasionally CHS, acted as effect modifiers of drug-outcome associations for certain medication classes. Relative to non-frail resident using the medication class of interest, pre-frail/frail individuals had an increased risk of hospitalization when using antipsychotic agents (adj. HR=2.30, 95%CI 1.43-3.70 and adj. HR=2.20, 95% CI 1.3-3.74, with frailty defined using FI and CHS, respectively), anticoagulants (adj. HR=1.64, 95% CI 1.06-2.53, with frailty defined using FI) and antiplatelet agents (adj. HR=1.66, 95% CI 1.15-2.38, with frailty defined using FI). The CHESS measure

was a weaker effect modifier. Pre-frail/frail residents using antipsychotic agents were also significantly more likely than non-frail antipsychotic users to reside in facilities with no licensed practical and/or registered nurse on site (25.5% vs. 13.6%) and with no pharmacist involvement in the past month (34.4% vs. 19.7%).

Conclusions: These findings suggest that frailty (particularly when measured using FI) may be a means of identifying older individuals vulnerable to drug-related adverse events. Clinical and policy-level interventions in AL settings may enhance quality of care and reduce hospitalizations among residents.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
NTW	Narrow Therapeutic Window
DAL	Designated (publicly-funded) Assisted Living
PIM	Potentially Inappropriate Medication
LTC	Long Term Care
ADR	Adverse Drug Reaction
HR	High-Risk
FDA	Food and Drug Administration
CIHI	Canadian Institute for Health Information
AGS	American Geriatrics Society
CHS	Cardiovascular Health Study
FI	Frailty Index
ADL	Activities of Daily Living
CHESS	Changes in Health, End-stage disease and Signs and Symptoms of Medical Problems
FRID	Fall-Risk Increasing Drug
HRME	High-Risk Medication in the Elderly
AL	Assisted Living
LPN	Licenced Practical Nurse
RN	Registered Nurse
ACE	Angiotensin Converting Enzyme
ACCES	Alberta Continuing Care Epidemiological Studies
RAI	Resident Assessment Instrument
ATC	Anatomical Therapeutic Chemical
ASA	Acetylsalicylic acid
Full FI	86-item Frailty Index
Armstrong FI	44-item Frailty Index
CHSabs	CHS measure with absolute cut-points
CHSrel	CHS measure with relative cut-points
CPS	Cognitive Performance Scale
CAP	Clinical Assessment Protocol
DRS	Depression Rating Scale
ABS	Aggressive Behaviour Scale
SD	Standard Deviation
RHA	Regional Health Authority
GP	General Practitioners
CI	Confidence Interval
HR	Hazard Ratio
GI	Gastro-intestinal

1. INTRODUCTION

The high burden of chronic illness in older individuals often results in high levels of medication use among this population.[1] Considerable comorbidity and exposure to high numbers of medications among older adults (with consequent drug-drug and drug-disease interactions) increase their risk for drug-related errors and adverse events.[2,3,4,5]

Physiological changes associated with aging influence pharmacokinetic processes (i.e., the ways in which the body absorbs, distributes and excretes drugs).[6] The heterogeneity in these processes and in the fitness of older adults,[7] along with considerable variability in comorbidity and concurrent medication use, present challenges in making generalizations about the appropriateness of medications. Further, older adults with significant comorbidity are rarely included as subjects in clinical trials, limiting the evidence that exists on safe prescribing in this population.[8,9,10,11]

Despite limitations in clinical trials, a strong base of epidemiologic evidence suggests that certain pharmaceuticals pose an increased risk in older adults.[12,13,14] Further research suggests that this risk is heightened for frail, when compared to robust (not frail), older individuals.[15, 16,17] Frail older adults are a subset of the older population who have a decreased capacity to recover from stressors.[18,19] Frailty has been conceptually linked with reduced physiologic reserves across multiple organ systems,[18,20] and as such, its presence could feasibly modify pharmacokinetic processes above and beyond the effects of aging. In fact, there is evidence that clearance of certain medications is reduced in frail individuals when compared to more robust older adults.[21,22] Depending on the frailty definition considered, cognitive, psychological and social vulnerabilities may also contribute to the identification of frailty in older

adults.[19,20,23] Cognitive, psychological and social concerns, including associated issues with medication administration and adherence, have a considerable impact on the safety of medication use.[24,25,26] For example, depressive symptoms and low social support have both been observed to be independently associated with reduced medication adherence in those with type 2 diabetes.[26]

Attempts have been made to identify drugs that are particularly dangerous in older adults, and thus are deemed inappropriate under any circumstances, or when considering potential drug-drug or drug-disease interactions. Sets of explicit guidelines have been developed to aid physicians when making prescribing decisions for older patients.[27,28,29] Several observational studies have explored the ability of such explicit criteria to identify potentially inappropriate medication use and predict adverse outcomes, with considerable variability in findings. Other evidence suggests that a greater risk of adverse outcomes comes from supratherapeutic effects of otherwise helpful medications.[30] Medications often implicated in such events are known as narrow therapeutic window (NTW) drugs and include warfarin, oral antiplatelet agents, insulin, and oral antidiabetic agents.[30] These drugs are appropriate and often necessary, but they pose serious risks if their use is not carefully monitored and adjusted as needed. Understanding the relative benefit/risk ratios of these drugs in older adults is important given the high rates of adverse events associated with their use.[30] Frailty status has been relatively unexplored in relation to medication-related adverse events, and may be particularly relevant in altering the benefit/risk profile of several important medications.

The overall aim of the present research was to investigate whether selected measures of frailty act as effect modifiers of associations between certain high-risk or potentially inappropriate medications and hospitalization risk in a vulnerable older population. Using linked clinical,

functional and administrative health data for a cohort of Designated (publicly funded) Assisted Living (DAL) residents aged 65+ years, associations between specific high-risk medication use and hospitalization during the 1-year follow-up period were examined, considering frailty as a potential effect modifier.

The present research is focused on the four high-risk medication classes mentioned above (anticoagulants, oral antiplatelet agents, insulins, and oral hypoglycemic agents). In addition to this, a fifth class of potentially inappropriate medications (antipsychotics) was examined. Antipsychotics warrant consideration because they continue to be commonly used despite serious risks for older frail populations.[31,32,33] Additionally, examination of antipsychotic medications allows for comparison with other drug-outcome studies that examined this class.

The present research addresses gaps in the literature with respect to the role of frailty in modifying the effects of high-risk and antipsychotic medication use. Additionally, this research explores frailty measures as a means of identifying those older adults who are most vulnerable to adverse drug events when using high-risk medications.

2. LITERATURE REVIEW

2.1 Pharmacotherapy Concerns in Older Adults

Suboptimal medication use puts older adults at heightened risk of morbidity and mortality[2,3,4] while adding to the burden on the health care system through increased levels of service use and cost.[34] Indeed, one study found that the estimated cost of emergency department visits and hospitalizations of older adults in Canada due to adverse drug reactions in 2007 was $35.7 million.[34] Older adults are at increased risk for sub-optimal prescribing due to frequent polypharmacy and comorbidities, as well as age-related changes in pharmacokinetics.[35]

The heightened variability in the health status of older adults, known as aged heterogeneity,[7] introduces further challenges to health care providers in making the correct prescribing decisions. Changes in body composition accompanying advanced age lead to an increased proportion of body fat, reduced lean muscle and decreased total body water, influencing absorption and storage of medications.[6] Additionally, clinically complex older adults often have impaired liver and kidney function, resulting in altered metabolism and excretion of medications, as well as altered permeability of the blood-brain barrier, and enhanced sensitivity to certain drugs.[6] At the same time, older adults with significant comorbidity are rarely included as subjects in clinical trials,[8,9,11] limiting the evidence that exists on the relative risks and benefits of selected drugs in this population.

2.1.1 High-risk/Potentially Inappropriate Medications

In an effort to identify potentially inappropriate drug use leading to adverse drug events, lists of medications which pose unnecessarily high risk in older adults have been developed. The Beers criteria, a list of potentially inappropriate medications (PIM) originally formulated by

consensus review in 1991,[36] are the most commonly used of these explicit lists. The Beers criteria have been updated three times[27,37,38] since their original development and have been applied under many circumstances from research to clinical prescribing decisions to federal regulations on long-term care (LTC).[39]

Published evidence is not consistent regarding the ability of the Beer's criteria to identify potentially harmful medication use. A limited number of observational studies have found an association between PIMs, as defined by the Beer's criteria, and adverse outcomes such as hospitalization, mortality, and diminished quality of life.[40-46] Other studies, in contrast, have found no significant associations between Beers list medications and adverse outcomes.[47-54]

In fact, using US nationally representative health surveillance data, one study[55] determined that only 3.6% of drug-related emergency department visits in older adults were associated with inappropriate drugs, as defined by the 2003 Beers criteria.[38] In contrast, three drugs (warfarin, insulin, and digoxin) were associated with one third (33.3%) of visits for adverse drug events.[55] In a later study,[30] the same group found that two-thirds (67%) of emergency hospitalizations resulting from adverse drug events in older adults were associated with four drugs or drug classes (warfarin, oral antiplatelet agents, insulin, and oral hypoglycemic agents). A Canadian study found that the drug class most commonly associated with hospitalizations related to adverse drug reactions (ADR) was anticoagulants (including warfarin) , accounting for 12.6% of ADR-related hospitalizations from 2006 to 2011.[56]

2.1.2 Narrow Therapeutic Window Drugs

The four drug classes which were observed by Budnitz and colleagues to be implicated in the majority of emergency hospitalizations (warfarin, oral antiplatelet agents, insulin, and oral

hypoglycemic agents)[30] are referred to as narrow therapeutic window (NTW) drugs. NTW drugs are medically necessary and beneficial when used correctly, but can cause substantial harm if drug administration and dosage is not monitored properly.[57,58,59] It seems likely that a greater risk of harm from NTW drugs would also be associated with a higher degree of clinical complexity, as potential drug-disease and drug-drug interactions would modify the benefit-risk profile of these drugs.

The challenge of medication management involved in the use of certain NTW drugs is illustrated by the observation of Lispka and colleagues that rates of hospital admission for hypoglycemia among diabetic older adults have exceeded rates for hyperglycemia between 1999 and 2010.[60] The authors point out that overall rates of hospitalization (after adjusting for increasing rates of diabetes) for both hypoglycemia and hyperglycemia have decreased since 2007, but hypoglycemia hospitalizations have decreased at a much slower rate. These findings offer evidence that the emphasis on lowering blood glucose levels in those with diabetes may have resulted in hypoglycemia surpassing hyperglycemia as the major adverse effect associated with diabetes treatment, suggesting that overtreatment of diabetes is potentially more concerning than under treatment. However, the authors maintain that both over- and under-treatment remain serious concerns.[60]

Similar challenges exist with regard to prescription and management of oral anticoagulant and antiplatelet medication. Low rates of prescription of these medications in patients with a history of stroke or atrial fibrillation has been identified as underprescription by some.[61,62] However, when considering the specific circumstances, many physicians consider long-term use of anticoagulant therapy to be inappropriate, placing patients at an increased risk of falls and bleeding.[63]

The term high-risk (HR) medication is often used in the literature to refer to NTW drugs and will be used primarily to refer to such medications for the remainder of the thesis document. NTW drugs can be considered HR medications because, unlike PIMs, they may be appropriate for some older adults and are often medically necessary, but also carry an elevated risk of adverse drug events.

2.1.3 Antipsychotic Agents

Despite the fact that PIMs, as a group, are implicated in few adverse drug events when compared to NTW drugs, certain drug classes included in the Beers list have relatively greater evidence of risk in vulnerable older adults. In particular, antipsychotic agents have been shown to be associated with adverse events including stroke,[32] sudden cardiac death [33] and falls [31,64] in older adults.

Antipsychotic agents are used for the management of psychiatric disorders, including schizophrenia and bipolar disorder. Antipsychotics are classified into the groups conventional or atypical, based on biological activity. Conventional antipsychotics block dopamine receptors, while atypical antipsychotics act on both dopamine and serotonin receptors.[65] In LTC settings, these agents are often used for treatment of psychiatric disorders, but are also commonly used to manage the behavioural problems associated with dementia, despite strong indications of increased risk of death (mostly due to stroke and sudden cardiac death) in those with dementia.[66,67,68] In fact, in 2005 both the US Food and Drug Administration (FDA), as well as Health Canada issued an alert stating that atypical antipsychotics (with the exception of risperidone, in the Health Canada alert) are associated with an increased risk of death in older adults with dementia.[69,70] In 2008, the FDA statement was expanded to include conventional antipsychotics, as well.[69] However, a US Department of Health and Human Services report

found that 83% of claims for atypical antipsychotic drugs were prescribed for off-label conditions (i.e., conditions other than those for which the drug was approved). In 88% of these cases, the drug was used for conditions which were cautioned against by the FDA (e.g., dementia).[71]

In a study of Ontario nursing home residents, Rochon and colleagues observed that approximately one-third of LTC residents were prescribed antipsychotic agents in 2003.[72] Despite similar resident characteristics across facilities, rates of prescription in different LTC facilities ranged from 20% to 40%.[72] Although this study was conducted prior to the release of the Health Canada alerts regarding antipsychotic use, subsequent research examined the impact of these alerts on rates of antipsychotic prescription. It was observed that following the release of the Health Canada alerts, growth in the use of atypical antipsychotics slowed; however, no reductions were observed in the overall rate of prescription of these drugs.[73]

Current data from the Canadian Institute for Health Information (CIHI) indicate that 30.3% of Canadian LTC residents were using antipsychotic drugs without a diagnosis of psychosis from 2013 to 2014.[74] This rate has been steadily decreasing from 34.1% in 2010. Similar to the observations of Rochon and colleagues,[72] CIHI reported considerable variation in prevalence of antipsychotic use across long-term care homes, ranging from approximately 1 in 5 residents to 1 in 2 residents. The reported rate of potentially inappropriate antipsychotic use in Alberta LTC homes was lower than the Canadian rate, with a 2013-2014 prevalence of 25.3%.[74]

The latest version of the Beer's criteria, updated by the American Geriatrics Society (AGS), recommends that antipsychotics not be prescribed to those with dementia.[27] Furthermore, certain antipsychotic agents can worsen the symptoms of Parkinsonism through their dopamine

receptor antagonist function,[75] and are not recommended for individuals with Parkinson's disease.[27] Additional evidence suggests a strong association between antipsychotic use and falls in older individuals.[31,64] Falls are a significant concern among older adults, associated with hospitalization, institutionalization, death, disability, reduced quality of life, and social isolation.[76] The AGS recommends that in all older individuals, antipsychotic agents should be used with caution.[27]

The high prevalence of antipsychotic medication use in nursing home and residential care settings,[71,72,74] along with the pervasive use of these drugs for off-label conditions and dementia,[71,74] suggest that antipsychotic use may be a source of concern in residential and LTC settings. The US Department of Health and Human Services reported that in 22% of Medicare claims for atypical antipsychotics in nursing homes, the drug was not administered in accordance with the standards set by the Centres for Medicare and Medicaid Services.[71] The drugs were either administered "in excessive dose, for excessive duration, without adequate indication for use, without adequate monitoring, or in the presence of adverse consequences that indicate that the drug should be reduced or discontinued." (Levinson, 2011).[71]

The concerns regarding inappropriate prescription, administration and monitoring of antipsychotic agents in LTC settings suggest a need for interventions to improve management of these medications. In particular, the evidence of risk associated with use of antipsychotics in many older, vulnerable populations (with or without dementia) indicates a need for a means of identifying those older individuals at highest risk of harm associated with antipsychotic use in order to emphasize the importance of caution with antipsychotic prescription and management in such groups. Similarly, given the high rate of adverse outcomes associated with use of NTW drugs, it is important that the use of these high-risk medications be monitored closely,

particularly in individuals who are most vulnerable to experiencing adverse drug events. The concept of frailty may offer an approach for the identification of older residential and LTC residents who are particularly vulnerable to adverse events from the use of HR medications and antipsychotic drugs.

2.2 Frailty

Although there is no universally acknowledged standard definition for frailty, the most widely accepted definition describes a reduction in physiologic reserves due to deficiencies in several inter-related systems, resulting in decreased ability to endure and recover from stressors.[23] Due to the multi-dimensional nature of this syndrome and the absence of definitive biomarkers, this definition is difficult to operationalize. Moreover, since the definition is based on an individual's response to a stressful or adverse event, identifying frailty prior to exposure to a stressor is an added challenge.

The concept of frailty as a result of reduced physiologic reserves is considered in a review by Bortz.[77] He explains that all organ systems feature redundancy such that the systems continue to operate properly, even when function decreases. Bortz identified several body systems that, when acting at 30% of normal function, continue to be operational. However, once the functionality of these organ systems drops below 30%, symptoms of damage become evident.[77] Based on this concept, frailty would be the state in which loss and damage to several body systems has exceeded the threshold of redundancy and evidence of these losses become apparent collectively as increased vulnerability to stressors.

The occurrence of damage to multiple body systems leading to the development of frailty in older adults may be explained by a theory of aging known as the Theory of *Inflammaging*.[78]

This theory suggests that an imbalance of pro-inflammatory over anti-inflammatory responses (possibly due to genetic and lifestyle factors) may lead to poorly controlled low-grade inflammation during aging, resulting in gradual damage to the body systems.[78]

Other models suggest a cycle of decline involving neuroendocrine dysregulation, immune dysfunction, chronic under-nutrition, and reduction in muscle mass (sarcopenia).[79] This cycle leads to impaired homeostasis and biological reserves, decreased physical activity and continued sarcopenic decline. The dysfunction of these biological systems contributes to development of frailty, and can be exacerbated by co-existing acute and chronic illness.[79]

Several measurement tools have been developed to identify and quantify frailty. The most commonly used of these measures is the *Cardiovascular Health Study* (CHS) criteria developed by Fried and colleagues.[80] Meeting 3 or more of 5 criteria (weight loss, low grip strength, slow walking speed, low physical activity, and exhaustion) indicates a frail phenotype, using this tool.[80] A more comprehensive measure developed by Rockwood, Mitnitski and colleagues is the Frailty Index (FI), which measures accumulation of health deficits. This tool assigns a score based on the ratio of the total number of deficits existing in an individual out of an inventory of potential deficits considered and/or measured.[81,82] The FI can consider a flexible list of deficits including diseases, functional impairments, signs, symptoms, and laboratory test findings, but should include at least 30 variables encompassing multiple organ systems.[81,83] The FI expands on the criteria considered in the CHS, incorporating aspects of clinical, social, functional, and psychological frailty, in addition to physical components. The FI shows high predictive validity,[82,84] but can be time-intensive. However, the FI measure can often be generated using pre-existing data sources, typically from the results of a comprehensive geriatric assessment. As noted in prior publications, if data from

such assessments are automated, the FI could be feasibly applied as a measure across many clinical settings.[85]

Through observational studies, frailty, as measured by both the CHS criteria and the FI, has been found to be independently associated with various adverse outcomes including falls and injuries, hospitalization, ADL disability, institutionalization, and death.[18,80,86,87] Additionally, both approaches consistently detect higher prevalence of frailty among women, and with increasing age. [79,80,84,86]

The *Changes in Health, End-stage disease and Signs and Symptoms of Medical Problems* (CHESS) scale is a tool derived from items included in the Resident Assessment Instrument (interRAI) group of instruments.[88] The interRAI instruments are standardized clinical assessments which are used across various health and social service settings to collect data on the characteristics and outcomes of those served.[88] The CHESS scale is intended for the measurement of instability in health status and, as with the frailty measures outlined above, can be used to identify vulnerability in older adults.[88] The CHESS scale was designed to identify residents at high-risk for decline in health status.[88] In studies of LTC residents, greater health instability, as determined by the CHESS scale, has been shown to be highly predictive of mortality and hospitalization.[88,89] The CHESS scale has been compared to established measures of frailty in existing publications, [85,90] and has also been suggested to act as a frailty measurement tool in others.[88,90]

In a recent editorial, Hubbard and Lang[91] discussed the frequent co-occurrence of frailty, depression and dementia in older adults and offered evidence suggesting that each of these conditions may lead to development or worsening of the others. They argue that improved

understanding of these conditions, their risk factors and the inter-relationships between them may allow for the development of interventions to reduce the prevalence of all three conditions.[91]

The concept of frailty (or other markers of vulnerability) may be useful for identifying older adults at risk for decline in health status, offering health care providers the opportunity to make informed choices regarding treatment and monitoring of patients, particularly with respect to pharmacotherapy.

2.3 Frailty and Medication Use

Potentially inappropriate medication use has been found to be highly prevalent among frail older adults,[92,93] as has polypharmacy,[17,94,95,96] and the occurrence of adverse drug reactions.[97,98] With conflicting evidence regarding the ability of explicit criteria such as the Beer's criteria to predict adverse drug events, frailty status may serve as a tool to identify individuals who are more likely to be vulnerable to adverse events when using potentially inappropriate medications. Additionally, with strong evidence suggesting that a high proportion of drug-related hospitalizations result from use of NTW drugs,[30,56] frail individuals may represent a portion of the population who are at particular risk and in need of targeted care and monitoring associated with the use of these NTW drugs.

The altered pharmacokinetics associated with the physical state of frailty have been investigated in studies which have found decreased gentamicin clearance in frail older adults compared to non-frail.[21,22] Physiologic changes associated with frailty, including changes in body composition (reduced muscle, and increased proportion of body fat), albumin levels, elevated inflammatory markers, and the accompanying changes in pharmacokinetic responses

to medications, may place frail individuals at higher risk of adverse drug events, when compared to robust older adults.[99-103] While there is evidence suggesting that changing pharmacokinetics may occur with frailty, increasing the risk of adverse drug events, there has been limited investigation regarding pharmacodynamics changes in frail older adults. Changes in pharmacodynamics would be expected to result in altered sensitivity to certain medications when frail individuals are compared to robust individuals. The paucity of data regarding pharmacodynamic changes in frailty further complicates individual and policy-level recommendations regarding pharmacotherapy in frail older adults.

When considering frailty as defined by the FI, cognitive, social and psychological concerns, in addition to physical deficits, contribute to frailty status. The cognitive, psychological and social aspects of frailty are likely to have a considerable impact on adherence, maintenance of correct dosage and overall medication management in frail older adults.[24-26] For example, medication non-adherence in older adults has been linked to depressive symptoms, [26] low social support,[26] and cognitive changes.[24] Additionally, unmet medication support needs have been linked to increased risk of hospitalization in older adults.[25] It has been suggested that guidelines for prescribing in healthy older adults are likely not suitable for frail individuals, and more research is needed to inform appropriate medication use in this group.[102,104]

Medication use in frail older adults is an emerging area of research, with very few publications considering the potential importance of frailty status as an indicator of vulnerability to drug-related adverse outcomes. Observational studies have noted that suboptimal pharmacotherapy increases the risk of hospital admission[105,106] and adverse drug reactions[97]among frail older adults. In the case of these studies, suboptimal pharmacotherapy includes polypharmacy,[97] therapeutic failure,[106] and inappropriate prescribing according to STOPP/START (an explicit

drug list, similar to the Beers criteria).[105] In all of these studies, frailty was not determined using any commonly accepted assessment tool, but was identified based on meeting a certain number of a list of frailty criteria (common elements include recent falls, limited functional capabilities, recent hospital admission and dementia).[97,105,106]

The studies mentioned thus far were focused on determining the prevalence of inappropriate medication use or adverse drug reactions in frail older adults. However, very few studies have examined inappropriate drug use in frail, compared to non-frail older adults, or sought to identify outcomes associated with suboptimal pharmacotherapy in frail older adults compared to their non-frail counterparts. In the studies that did examine these issues, it was observed that frail older adults are prescribed more inappropriate drugs than non-frail members of the same population,[16,17] and that suboptimal pharmacotherapy is associated with greater risk of hospital re-admissions,[15] falls,[16,17] and poor functional outcomes[17] in frail older adults when compared to non-frail older adults.

Of those studies, one [17] considered only polypharmacy as the medication exposure of interest; one[16] considered polypharmacy, drugs associated with an increased risk of falls (Fall Risk Increasing Drugs, FRIDs) and potential drug-drug interactions;[107] and the other[15] utilized an explicit list of High-risk Medications in the Elderly (HRME),[29] similar to the Beer's criteria. Given the evidence suggesting that the majority of adverse drug events result from use of NTW drugs,[30] an important next step in the research into frailty and medication use would be an examination of the effect of frailty on adverse events related to NTW drug use.

Of the studies considering drug-related adverse events in frail older adults compared to robust older adults, the measures of frailty used differed considerably. One study[16] utilized the

Edmonton Frail Scale, one[17] used the FI, and another[15] designated frailty based on the presence of one or more conditions (coagulotherapy, involuntary weight loss, fluid and electrolyte imbalance, anemia, and fall or fracture) that have been observed to be associated with CHS frailty status in prior studies. Although many valid tools exist for identifying frailty, the CHS frailty criteria and the FI represent two distinct views of frailty: frailty as a physical phenotype (CHS), or frailty as an accumulation of deficits, including physical, psychosocial and clinical concerns (FI). Another important gap in current research is a comparison of these key conceptualizations of frailty with respect to identifying which measurement tool may be best able to predict the occurrence of particular outcomes associated with medication use.

Bennett and colleagues[16] observed that frail participants were more likely to use a higher number of FRIDs, to use a higher number of drugs, and to have potential drug-drug interactions. They also found that falls are likely to occur in frail individuals taking fewer concurrent FRIDs (falls predicted at 1.5 FRIDs) when compared to robust individuals (falls predicted at 2.5 FRIDs).[16] In the study by Pugh and colleagues,[15] an interaction effect was observed between frailty-related diagnoses and chronic use of HRME. Individuals without frailty-related diagnoses using chronic HRME were protected from hospital re-admission, while those with frailty-related diagnoses using chronic HRME were not protected. However, in this study, no interaction was observed between incident HRME use and frailty-related diagnosis. Rangunga and colleagues[17] found that frailty (as defined by the FI) mediated the relationship between polypharmacy and adverse outcomes (including poor functional outcomes and falls). A summary table of these studies is given in Appendix A.

A study involving the use of oral anticoagulants in older adults with atrial fibrillation offers evidence that use of NTW drugs may present particular challenges with regard to medication

management and monitoring in frail older adults. Perera and colleagues[108] found that frail patients were significantly less likely to be prescribed warfarin upon hospital admission or discharge. After six months, frail patients were significantly more likely to experience an embolic stroke compared to non-frail patients (RR 3.5, 95% CI 1.0-12.0), but also had a small non-significant increase in the risk of major hemorrhage (RR 1.5, 95% CI 0.7-3.0).[108] The unique characteristics of frail older adults lead to a complex set of risk factors with regard to anticoagulant medication use and the balance between stroke prevention and bleeding risk.[109,110]

Additionally, with respect to antidiabetic medications, vulnerable older adults have been found to experience different outcomes compared to less vulnerable older adults. The odds of hypoglycemia have been reported to be particularly elevated in those with dementia when using sulfonylurea or combined metformin and sulfonylurea (oral antidiabetic agents), with more favorable odds reported for dementia patients using insulin.[111] Given the high rate of dementia in continuing care facilities, the inconsistencies in risk associated with diabetes medications in those with dementia compared to those without may be particularly relevant in such populations. Additionally, given the fact that dementia has been found to overlap considerably with frailty,[91] it may be relevant to explore the impact of frailty on risk associated with use of these medications.

The issues surrounding frailty and medication management are likely to be an emerging quality of care concern for older residents of residential care facilities (including assisted living [AL]), given the growing reliance on such facilities to accommodate increasingly vulnerable older adults.[112,113,114,115] As argued in the following sections, despite the increasing reliance on AL facilities for care of clinically complex older adults (including residents with dementia and

related disorders), these facilities have been the subject of limited research, particularly in Canada.

2.4 Assisted Living

Assisted living describes a broad range of group residential settings offering care and support to older adults. [116,117] Assisted living facilities differ from retirement homes, because they offer a higher level of care, including assistance with activities of daily living and some degree of assistance with health needs.[116,117,118] These facilities do not fall under federal regulations for LTC, and thus, are distinct from nursing facilities.[116,117] In general, assisted living facilities are often regarded as an alternative to nursing home care for those older adults without complex medical needs who require support, but desire a comfortable, home-like atmosphere, in contrast to the institutional setting of LTC.[116,118]

The broad array of assisted living facilities available results in considerable diversity in resident case-mix as well as level of care offered between different facilities.[119,120] Despite the fact that AL facilities are generally considered to offer supportive residential care for older adults without complex medical needs, research studies have revealed that many AL residents have significant physical, cognitive and functional concerns.[112,113,114,115] Additionally, clinical complexity among assisted living residents may increase over time. Indeed, certain assisted living facilities ascribe to the concept of 'aging in place', which emphasizes the idea that residents should be able to remain at the assisted living facility as they age, rather than being transferred to LTC. As a result, the complexity of care required in these settings will increase over time as residents age.[121] This is of particular concern as AL facilities tend to employ fewer licensed nurses and have fewer hours of skilled staffing on average, when compared to LTC facilities.[112,120,121,122]

Most knowledge regarding assisted living has been based on US research. As AL has become increasingly popular in Canada over the past 5-10 years, Canadian researchers have identified similar concerns to those expressed in previous US studies.[112,120,123] In both Canada[117] and the US,[118] there is limited government standardization and considerable variability between AL facilities. As such, there is concern that limited skilled staffing could result in decreased detection and poorer management of health concerns, and a resulting increased risk of hospitalization.[112,120,121,122,124] This concern is well represented by a study comparing various AL facilities across Maryland in which it was found that residents with higher levels of comorbidity were no more likely to be in a facility with higher levels of skilled staffing per resident, higher facility level-of-care certification, a licensed nurse on staff, or a physician who made regular visits to the facility.[113] The annual incidence of hospitalization from assisted living facilities across Alberta was reported to be 38.9%,[112] with similar rates reported in two American studies.[122,125] In contrast, the annual incidence of hospitalization from LTC facilities in the same Alberta study was considerably lower at 13.7%.[112] Although this may reflect better care and disease management in LTC facilities, it may also be related to the general higher severity of disease among LTC residents (leading to a greater reluctance to hospitalize) and/or the existence of advance directives discouraging hospitalization of these patients.[112]

Despite the existence of the 'aging in place' philosophy in many assisted living facilities, research has indicated a relatively high rate of admission to LTC from Alberta AL facilities (an annual incidence estimated at 18.3%).[120] This is a source of concern due to the high risk of adverse outcomes associated with care transitions in older individuals.[126,127]

The high proportion of AL residents with dementia and mental health concerns reported in both US[113,114,115] and Canadian[123] literature adds to concerns regarding the capability of AL

facilities and staff to manage resident needs. In Alberta this is of particular concern due to the 2008 continuing care reform strategy which proposed AL as a substitute for LTC for those individuals with lower care needs.[128] Conversely, in Ontario and British Columbia, AL is primarily considered an option only for those without significant physical or cognitive impairment.[129,130] However, as the demand for LTC surpasses availability, assisted living facilities across Canada may begin to take on residents with increasingly complex care needs.

The limitation in skilled staffing in AL facilities in the face of increasing complexity of residents is a cause for particular concern when considering the issue of medication oversight and management.

2.5 Assisted Living and Medication Management

Several studies have identified medication prescription and management as an area for improvement in AL facilities.[113,131,132,133] A Maryland study showed that the average number of medications prescribed to AL residents was 4.5[113] while a later study from Alberta found an average of 8.3 prescriptions per AL resident.[112] Interview-based studies have found that medical professionals have reported a lack of confidence that AL staff are adequately trained to properly manage the complex care and medication management needs of residents.[134,135] This is an area of concern considering that AL staff are often responsible for the administration of prescription medications to residents. The Maryland study found that AL staff carried out medication administration for 87.4% of residents.[113]

Issues surrounding medication management are especially concerning considering the lower levels of licensed nursing care available in AL compared to LTC.[112,120,121,122] The majority of health care staff in AL facilities are non-nurse health care aides (including nurse's aides and

personal support workers),[112,120,121,122] who may have very little training in terms of clinical and medication management of residents. Some AL facilities also employ more highly trained, licensed nurses including Licensed Practical Nurses (LPNs) and Registered Nurses (RNs, who have the higher level of training and skill set, compared to LPNs). In a study of 11 AL facilities in South Carolina and Tennessee, it was found that the odds of medication errors for non-nurses were twice as high as the odds among LPNs or non-nurses trained as medication aides.[132] Despite the general shortage of licensed care in AL facilities, one AL study found that half of residents were receiving a medication that generally required additional monitoring.[113]

Observational studies have revealed error rates of 28-42% in medication administration in AL facilities.[131,132] However, these rates reduced to 8-20% when excluding timing errors.[131,132] One of these studies[132] found that 7% of medication administrations had moderate or high potential for harm, while the other[131] found that only 0.2% of medication administrations observed had potential clinical significance. Both studies reported that the errors with the greatest potential for harm commonly involved administration of insulin or warfarin (two NTW drugs).[131,132] Warfarin and insulin were also identified as drugs commonly involved in errors in nursing home settings.[136]

Another study of AL facilities in Florida, Maryland, North Carolina and New Jersey used a modified version of the Beer's criteria to identify that 16% of residents were receiving inappropriate medications.[137] The high levels of inappropriate prescribing may be explained by low physician involvement in many AL facilities. A study of antibiotic prescription to AL residents demonstrated that prescribing physicians often had limited knowledge of the resident and were often unaware of the level of support available through family members or AL staff.

Additionally, in 21% of cases of antibiotic prescribing, it was found that the physician did not examine the resident prior to prescribing.[138]

Other studies have noted underprescription of drugs in assisted living including such drugs as angiotensin-converting enzyme (ACE) inhibitors, anticoagulants and antiplatelet agents, aspirin, and beta-blockers,[61] as well as medications for dementia and psychiatric disorders.[115] Underprescription may include prescription of an inadequate amount of medication, or no prescription for a necessary or beneficial medication, and is an important consideration of suboptimal pharmacotherapy.

An earlier study based on the ACCES cohort[112] determined that a higher overall drug number (particularly 11+) in AL residents was found to be a significant risk factor for hospitalization after adjusting for potential confounders. Further work with this cohort is needed to examine which drugs may be linked to hospitalization risk and whether any observed risks are modified further by frailty.

As the complexity of AL residents increases and with the shortage of skilled staffing and limited services, it may become important to have a means of identifying particularly vulnerable residents who will require additional skilled support and monitoring in the areas of medication prescribing, oversight and management within this setting. Providing additional support to these vulnerable residents may improve health outcomes and decrease adverse drug events, leading to reduced need for health service use, particularly hospitalization, among AL residents.

2.6 Predictors of Hospitalization from Assisted Living and Long-term Care

Although sometimes appropriate, hospitalizations can be detrimental to the health of older adults, and represent significant cost to the healthcare system.[139] At the patient level, adverse outcomes associated with hospitalization of older adults include delirium, dehydration, falls, medication problems, and psychological distress associated with a change of setting.[140,141,142] In a US study, Mor and colleagues[143] comment on issues in care coordination between nursing facilities and hospitals by pointing out the high rates of re-hospitalization among nursing home residents. In this study, it was found that, following a hospitalization event, nursing home residents had a 30 day re-hospitalization rate of 26.8% in 2006.[143] The Medicaid reimbursement costs of these re-hospitalizations amounted to approximately $2.23 billion.[143]

There is a strong base of evidence suggesting that many hospitalizations from LTC and AL could be prevented with increased monitoring of residents and timely care provision.[144,145,146,147]

2.6.1 Assisted Living

Previous publications from the Alberta Continuing Care Epidemiological Studies (ACCES) study have concluded that there is a higher risk of hospital admission from DAL in residents with health instability (as indicated by CHESS score).[85,112] Additional factors found to be associated with higher risk of hospitalization in the ACCES study included moderate to severe fatigue, hyperpolypharmacy (11 or more medications), and at least 2 hospital admissions during the previous year.[112] There was also a slightly higher risk of hospital admissions in residents aged 90 or older and those with poor social relationships.[112] Another study revealed an increased risk of hospitalization in AL residents with higher Charlson comorbidity scores, those without an available informal caregiver, and those who were incontinent.[148] Lower

skilled staff hours were also found to be associated with higher risk of hospitalization in assisted living.[121,122]

2.6.2 Long-term Care

In LTC settings, factors that have been found to be associated with risk of hospitalization include male gender,[149,150] non-white race,[144,145] increased comorbidity,[144,151] higher number of prescriptions,[149,150,152] previous hospital admission,[146,150,152] and for-profit status of the facility.[145,152,153] The evidence regarding dementia as a risk factor for hospitalizations from LTC has been contradictory. Two studies found that risk of hospitalization would tend to increase with physical comorbidity, but would actually decrease among those with Alzheimer's or dementia.[150,154] In contrast, other studies showed dementia to be associated with higher risk of hospitalization.[121,145]

In relation to facility-level factors, lower skilled staff hours were found to be associated with higher risk of hospitalization in LTC.[149,155,156] Specifically, one LTC study found an inverse association between skilled staff hours and risk of avoidable hospitalizations only, with no difference in risk of unavoidable hospitalizations.[152] Some studies of LTC facilities, in the US, have also identified reimbursement policies as a key factor in determining the risk of hospitalization among residents.[143,152,157] That is, in some cases, facilities, residents or families may have a financial incentive for choosing hospitalization over care in the LTC facility. [143,152,157]

Evidently, there is a diverse range of factors contributing to the risk of hospitalization among older adults in continuing care, including sociodemographic factors, health status, previous health service use, medication use, facility factors, financial incentives, and others. An

independent means of identifying those at highest risk for hospitalization when using certain high-risk medications could allow for the introduction of interventions to not only improve the health of the resident, but also reduce unnecessary hospitalizations.

3. STUDY RATIONALE AND OBJECTIVES

With substantial comorbidity, high levels of medication use and age-related physiological changes, older adults are at an increased risk of drug-related errors and adverse events.[2,3,4,5,35] Existing research into explicit measures of potentially inappropriate medications (PIM) has shown conflicting evidence regarding the ability of these measures to predict adverse outcomes among older adults.[40-54] The present research will address this gap by exploring the use of frailty as a marker of vulnerability which can be used to identify those older adults who are at increased risk of harm associated with the use of high-risk or potentially inappropriate medications.

The following research focuses on high-risk (HR) drugs, those medications that are medically necessary under many circumstances, but have been associated with adverse events in older adults. Specifically, these drugs include the following narrow therapeutic window (NTW) drug classes: anticoagulants, oral antiplatelet agents, insulins and oral hypoglycemic agents. Use of antipsychotic agents, a class of potentially inappropriate medication (PIM), was also considered as a medication exposure of interest due to the high prevalence of antipsychotic use in long term care (LTC) and residential care settings[71,72] and high potential for risk associated with stroke, cardiac death and falls in vulnerable populations of older adults.[31,64,65] The NTW drugs of interest, antithrombotic and antidiabetic agents, are necessary for the management of cardiovascular disease and diabetes; however, errors in dosage and timing of administration as well as a failure to adjust prescriptions based on need, can lead to adverse events.[57,58,59] NTW drugs have been shown to be responsible for the majority of drug-related hospital admissions.[30] Given the high risk associated with these necessary medications, it is important to improve the medication management and monitoring for individuals at risk of adverse drug events.

However, no published research has suggested a means of identifying older adults who have an increased risk of adverse outcomes when using these high-risk medications. This research considers frailty as a means of identifying those older adults who are particularly vulnerable to adverse events related to high-risk medication use, and who thus may require additional monitoring. Two measures for identifying frailty were considered (the CHS Frailty criteria and the FI), as well as another marker of health instability (the CHESS scale) in order to consider which method of identifying vulnerability was best able to predict the outcome of interest.

The primary outcome of interest is hospitalization. Hospital admission of vulnerable older adults is associated with high risk of negative outcomes, including delirium, falls, and medication problems, [140,141,142] as well as substantial cost to the health care system.[139] Recent research points to the relevance of this outcome for this research, with the observations that NTW drugs[30,55] and frailty[85] may increase risk for hospitalization. Additional research shows high rate of hospitalization events from AL settings.[112,122]

The study population consists of residents of designated (publicly funded) assisted living (DAL) facilities in the province of Alberta. As the Canadian population ages and more individuals are in need of supportive housing, assisted living facilities are becoming an increasingly important residential care option.[117] Despite the growing need for assisted living, there is an absence of comprehensive regulation at the national and provincial levels.[117] Additionally, there has been very little Canadian research into the characteristics of these facilities and the health outcomes of residents. Of the available Canadian and U.S. research, there is strong evidence suggesting that assisted living (AL) facilities employ fewer licensed nurses per resident when compared to LTC facilities.[112,120-122] However, residents of AL tend to have high levels of physical and cognitive comorbidity as well as considerable functional

needs.[112-115] The current research will make an important contribution to the small base of Canadian literature considering the AL setting. Specifically, this research involves investigation of the important issue of outcomes associated with high-risk and antipsychotic medication use in assisted living settings. Given the evidence suggesting low levels of skilled staffing in AL facilities,[112,120-122] it is particularly relevant to consider safety of medication management in this setting. This research will investigate whether a frailty measure could be used to identify AL residents who are most vulnerable to adverse drug events, and thus require additional monitoring by skilled staff.

As stated previously, the aim of the current research is to investigate whether selected measures of frailty act as effect modifiers of associations between certain high-risk and antipsychotic medications and health outcomes (with a particular focus on hospitalization risk) in a vulnerable older population. In order to examine this question, linked clinical, functional, facility-level and administrative health data for a cohort of DAL residents aged 65+ years was used to address the following objectives:

1a. Examine [at baseline] the frailty status of DAL residents, as identified by three measures of vulnerability (the CHS frailty criteria, the Frailty Index, and the CHESS scale), and the resident-level correlates of frailty status;

1b. Examine [at baseline] the distribution in the use of specific high-risk medications (anticoagulants, oral antiplatelet agents, insulins, and oral hypoglycemic agents) and a class of potentially inappropriate medications (antipsychotic agents) by resident-level characteristics and frailty status (as identified by three measures of vulnerability);

2a. Examine associations between frailty status (as defined by three measures of vulnerability) and first-event hospitalization during a 1-year follow-up;

2b. Examine the associations between exposure to antipsychotic and high-risk medication classes and first-event hospitalization during a 1-year follow-up;

3. Determine whether frailty measures act to modify the associations of antipsychotic and high-risk medication use with hospitalization during the 1-year follow-up.

4. METHODS

4.1 Data Source: The Alberta Continuing Care Epidemiologic Studies (ACCES)

4.1.1 Study Population

The Alberta Continuing Care Epidemiologic Studies (ACCES) program was a longitudinal study consisting of baseline assessments and 1-year follow-up assessments of residents of designated (publicly funded) assisted living (DAL) and long-term care (LTC) facilities across Alberta from 2006-2009. In addition to resident data, the assessments also included data collection from family caregivers and facility representatives. Of 60 eligible DAL facilities, 59 facilities agreed to participate in the study.[158,159]

All eligible DAL residents from the 59 facilities were approached for participation. Exclusion criteria included age less than 65 years, recent admission (<21 days) or receiving palliative care. Of 1510 eligible DAL residents from the 59 facilities, 1089 consented to participate in the study (response rate = 72%). Of those not enrolled, 339 (22.5% of all eligible residents) refused to participate, and for the remaining 82 (5.4%), the legally designated surrogate could not be contacted. A similar age and sex distribution to that of participants was observed for the 364 (86.5%) nonparticipants for whom age and sex data were available (mean age 84.4 ± 7.1 years, 74% women).

In addition to baseline and 1-year follow-up assessments, participants or surrogate decision makers provided consent allowing investigators to access residents' health utilization data for 1069 residents (98% of participants).

4.1.2 Data Collection

Baseline and 1-year follow-up assessments of residents were carried out by trained research nurses, who administered the Resident Assessment Instrument for Assisted Living (interRAI-AL see www.interrai.org/instruments.html). The interRAI-AL captures information on residents' sociodemographic characteristics, health conditions, physical and cognitive status, behavioural problems, and use of medications and services. These assessments were carried out using information obtained directly from the resident, as well as information from family caregivers, staff members and chart review.

For each participating DAL facility, a facility representative (facility administrator, manager, or director of care) assisted in the completion of the facility survey which included questions related to the following subjects: location, ownership, type and size of the facility, admission and retention criteria, staffing, health and wellness services, hospitality services, physical and social environment, fees, and challenges facing DAL or LTC.

In the case of discharge or death of a participant prior to the 1-year follow-up assessment, a discharge tracking form given to the facilities was to be filled out and returned to the study coordinators. At this point, the study coordinators would contact a family caregiver to coordinate a discharge or decedent interview. Additionally, a Moves Addendum was added to the family caregiver interview of the 1-year follow-up assessment for any participant who had died or moved within the follow-up period. Generally, the most trusted information regarding participant discharge or death was obtained from facility files.

If consent was provided by participants, study coordinators accessed health service utilization data from Alberta Health and Wellness and Regional Health Authorities. This included

information related to hospitalizations, emergency room visits, and day procedures. This health utilization data was linked with the resident-level data from the interRAI-AL assessment and facility records.

4.2 Analytic Sample

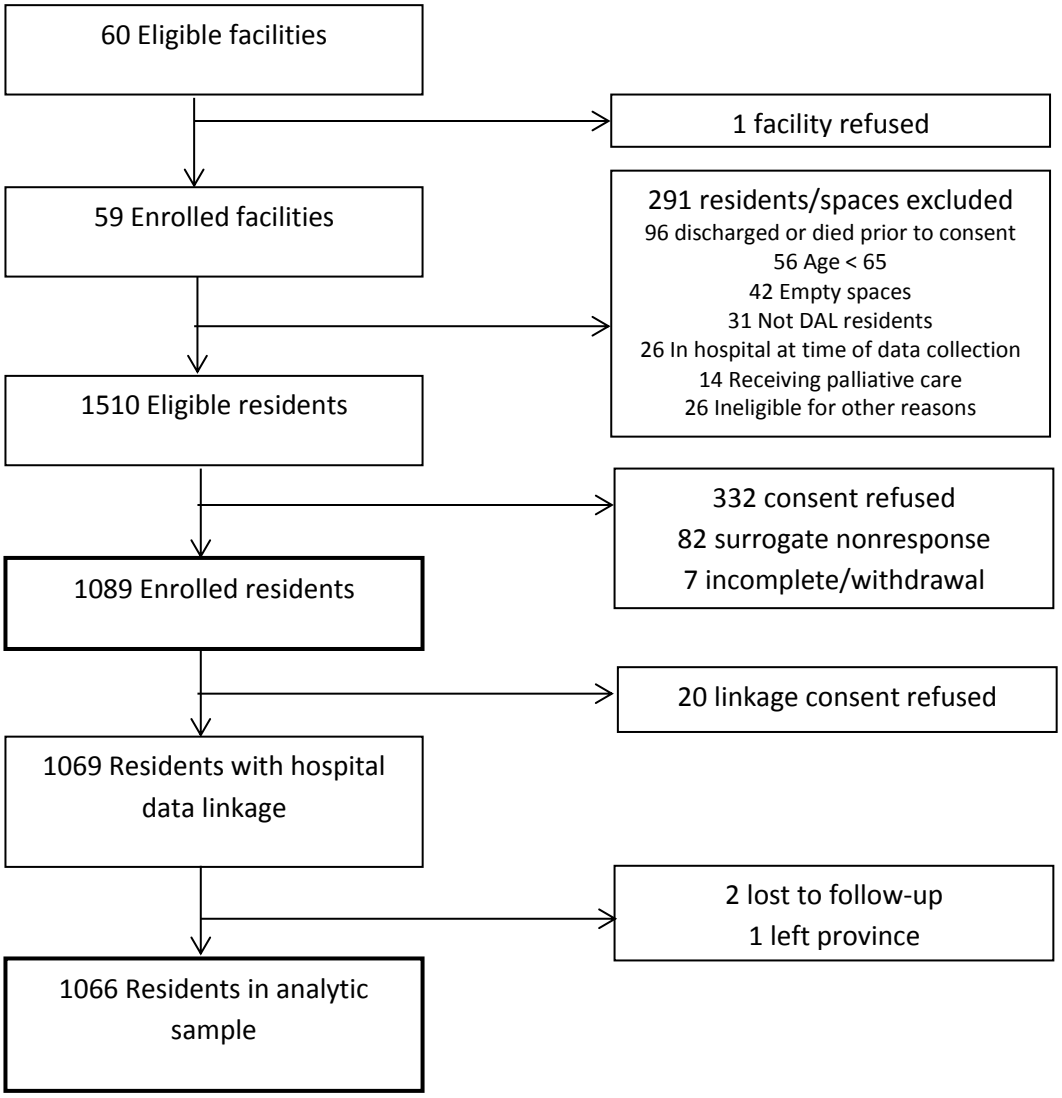
For the present research, the analytic sample consisted of the subset of ACCES participants residing in DAL facilities.

For descriptive analyses and Objective 1, the full cohort of 1,089 residents was included in the analytic sample because complete data was available to address this objective for all enrolled residents. One exception was in the examination of baseline characteristics, in which case both the full cohort of 1,089 residents and a sub-cohort of 1,066 residents were shown in order to compare the distribution of key resident and facility characteristics in the sub-cohort. The sub-cohort of 1,066 residents consists of those enrolled participants with a known outcome over the 1-year follow-up who provided consent for linkage with their health utilization data. This sample of 1,066 residents serves as the analytic sample for Objectives 2 and 3. Access to health utilization data is necessary for completion of these objectives because hospitalization is the outcome of interest.

Due to issues with the feasibility of applying the CHS measure to a vulnerable population, (an important limitation of the CHS approach, as noted in a previous publication)[123] missing data prevented determination of CHS frailty status for some residents. For those analyses involving the CHS frailty measure, the CHS cohort of 946 residents was the analytic sample for descriptive analyses and Objective 1, while the linkage consent cohort of 930 served as the analytic sample for Objectives 2 and 3.

The reasons for inclusion and exclusion of residents are shown in Figure 4.2.1, along with the numbers of residents meeting criteria for inclusion in the sample.

Figure 4.2.1. Flow Diagram of Analytic Sample from ACCES DAL Cohort



4.3 Measures

4.3.1 Exposures of Interest (High-risk Medications and Antipsychotics)

The primary exposure of interest for the current research includes measures capturing the use of narrow therapeutic window (NTW) drugs (including oral anticoagulants, oral antiplatelet agents, insulins, and oral hypoglycemic agents) and antipsychotic drugs at baseline. The specific medications that are included in these drug classes were identified using the literature,[30] provincial drug formularies, and a review of all medications used by DAL residents at baseline.

A comprehensive list of all active prescribed and non-prescribed medications taken by the resident in the last 3 days was captured in the interRAI-AL assessments administered by research nurses. Data items included drug name, dose, route of administration, frequency of administration, and how the drug was administered (i.e., by self, by assistive device, by family member, by RN, by LPN, by aide, or other).

The original drug records were translated into the Anatomical Therapeutic Chemical (ATC) classification system for ease of identifying specific therapeutic classes and subclasses of medications. In the ATC classification system, drugs are coded into five levels based on their active substance.[160] The drugs are categorized, first, based on the organ system on which they act, and are assigned a corresponding letter as the first digit of the code (e.g., N for nervous system). The next level of classification is based on the pharmacological/therapeutic subgroup and corresponds to a two-digit number, occupying the next two digits of the code (e.g., N05 for psycholeptics). The third and fourth levels are used to classify the chemical/pharmacological/ therapeutic subgroups and each corresponds to a different letter, providing the next two digits of the code (e.g., N05A for antipsychotics; and N05AE for indole derivatives). The fifth and

final level defines the specific chemical substance and is represented by a two-digit number which provides the last two digits of the ATC code (e.g., N05AE04 for ziprasidone).[160]

The ATC codes corresponding to the medication classes of interest (i.e., the first four digits of the ATC code) were used to search out and identify all of the medications within each class from the drug records in the ACCES database. The medication classes of interest and the corresponding ATC codes are shown in Appendix B.

The use of any of the high-risk medication classes of interest was captured using a variable coded as: 0 (no use of any high-risk medication classes), 1 (use of medication(s) from 1 high-risk medication class), and 2 (use of medications from 2 or more high-risk medication classes). Use of the high-risk medication classes was also captured with binary variables for each drug class (anticoagulants, oral antiplatelet agents, insulins, and oral antidiabetic agents) coded as: 0 (no use of any drugs within the selected class) vs 1 (use of 1 or more drugs within the selected class). Due to low numbers of residents using antidiabetic medications, use of any diabetes medication (insulin and/or oral antidiabetics) was explored as a binary summary variable. An additional binary variable defined by use of insulin and/or sulfonylurea was explored due to the particularly high hypoglycemia risk associated with use of insulin and with use of sulfonylurea.[59,111] In addition to the binary variable, use of oral antiplatelet agents was also explored as a three level categorical variable, in order to elucidate the effects of acetylsalicylic acid (ASA) and non-ASA antiplatelet agents, with the following coding scheme: 0 (no use of any oral antiplatelet agents), 1 (use of ASA antiplatelet agents with or without non-ASA antiplatelet agents), and 2 (use of non-ASA antiplatelet agents only). A binary variable was employed to capture residents' use of antipsychotics (PIM class under study) and was similarly coded as 0 (no use of any antipsychotic agents) vs.1 (use of 1 or more antipsychotic agents).

4.3.2 Frailty Measures

Frailty was considered as an independent variable of interest and as a possible effect modifier of the association between high-risk medication use and hospitalization in DAL residents. Frailty was hypothesized to act as an effect modifier because a resident's level of frailty may be associated with pharmacokinetic and pharmacodynamics changes,[21,22,99-103] or decreased ability to manage medications,[24-26] leading to a greater risk of adverse events and hospitalization when considering use of certain high-risk medications. Two separate measures of frailty were examined in the present research, specifically the Cardiovascular Health Study (CHS) criteria for frailty and the Frailty Index (FI). Both measures may be derived from data captured by the interRAI-AL assessment and are of interest in the present research as they represent two distinct approaches to (and conceptualizations of) frailty. Consequently, they may be expected to have varying effects as possible effect modifiers of any observed associations between the selected high-risk medications and hospitalization.

An 86-item frailty index[82] was derived from the interRAI-AL (see Appendix C) based on the methodology utilized by Searle et al,[83] and largely consistent with the 83-item index used in a previous ACCES publication, designated the *Full Frailty Index* (Full FI).[85] Additionally, a 44-item frailty index was derived also from the interRAI-AL (see Appendix D) based on the report by Armstrong et al,[90] and mostly consistent with the 43-item frailty index designated the *Armstrong Frailty Index* (Armstrong FI) in a previous ACCES publication.[85] Consistent with other studies,[83,85,161] for each frailty index, a score of less than 0.2 was selected to capture robust participants, while scores in the range of 0.2-0.3 indicate pre-frail status, and scores greater than 0.3 indicate a frail participant.

The CHS method identifies frailty using the following five criteria: slow gait speed, muscle weakness, unintentional weight loss, low physical activity, and exhaustion (see Appendix E). [80] Absence of these criteria indicates that the participant is robust, while presence of one or two of the criteria denotes pre-frail status and three or more indicates frailty.[80] Two versions of the CHS criteria were employed to assess whether residents were considered impaired for select criteria (gait speed, grip strength, physical activity). One, referred to here as the CHS absolute cut-points (CHSabs), used the cut-points specified in the original CHS frailty assessment.[80] The other, referred to as the CHS relative cut-points or CHSrel, was based on the score for each resident relative to the cohort, and identified the poorest performers for each of these criterion, within the study population, as determined in a previous ACCES study[123] (see Appendix E).

Resident status for three of the CHS criteria (unintentional weight loss, low physical activity and exhaustion) can be determined using pre-existing interRAI-AL questions. The CHS performance measures (gait speed test and grip strength test) were added as a supplement to the resident assessments in ACCES. However, data on all five CHS frailty criteria were unavailable for almost 40% of participants due to issues with the feasibility of assessing the CHS criteria in a vulnerable population.[123] Comments from research nurses indicated that missing values usually occurred when residents refused or failed to comprehend what was requested. This is likely explained by the high proportion (58%) of participants with dementia in the DAL cohort. In order to supplement missing data for those residents missing information, observed functional and health items from the interRAI-AL assessment were substituted, in the following manner.

For residents missing data on gait speed, if the research nurses documented that at least "limited assistance" was required with "walking between locations on the same floor indoors" and that "in the last 3 days the longest distance walked without sitting down was less than 5 meters", the resident was coded as impaired. If research nurses indicated that the reason for missing grip test data was that the resident was physically unable to perform the grip test, the resident was coded as impaired. Missing data on weight loss and exhaustion were supplemented based on yes/no responses to interRAI-AL items as assessed by research nurses. A positive response to the item, "Subject has had weight loss of 5% or more in last 30 days, or 10% or more in last 180 days" was used for weight loss while a positive response to the item "Due to diminished energy, is unable to finish normal day-to-day activities, or start some or any normal day-to-day activities" was used for exhaustion. Using these modifications, the proportion of participants with missing data for the CHS frailty assessment was reduced to 15%.

In addition to the two measures of frailty, the inter-RAI *Changes in Health, End-stage disease and Signs and Symptoms of medical problems* (CHESS) scale was also used to stratify participants by health stability status using items from the interRAI-AL assessment (see Appendix F). The interRAI-AL did not include two out of six symptoms that were originally included in the CHESS scale. Therefore, these two symptoms (dehydration, and decline in food/fluid intake) were not included in the symptom component of the CHESS score. Although CHESS is not specifically a frailty measurement tool, it has been shown to be predictive of mortality and hospitalization.[85,88-90] In order to present CHESS scores in a comparable fashion to frailty scores, the 5-point scale were condensed into a 3-point scale, as described by Hogan

et al.[85] A score of 0 will indicate low risk for serious decline, a score of 1 will indicate intermediate risk, and a score of 2 or more will indicate high-risk.

For initial analyses (Objective 1a), the two versions of each frailty measure were considered (CHSabs, CHSrel, Full FI and Armstrong FI), as well as the CHESS scale, and a one-item measure of fatigue, in order to identify the vulnerability measures best suited to the sample population and best able to predict hospitalization. For further analyses, the three frailty (or vulnerability) measures that were judged to be best suited to the sample population and to the research objectives were selected. These measures were the CHSrel frailty mearsure, Full FI and CHESS. For some descriptive analyses, findings for only these three key frailty measures are shown. Where it is relevant for understanding the selection of the final key measures, other descriptive tables include findings for all frailty (or vulnerability) measures.

4.3.3 Outcome

Time to first admission to an acute care hospital within 1 year of the baseline assessment was the primary outcome of interest. Hospitalization events were determined using the Alberta Inpatient Discharge Abstract Database, which has been linked to resident assessment data. The first discharge event associated with an admission to acute care will be assessed, rather than total hospital admissions. This stipulation was meant to address the possibility that residents may move from the original setting, and thus any subsequent admissions could reflect characteristics of the new location.

4.3.4 Covariates

Appropriate covariates were chosen from the sociodemographic, functional, and clinical items available from the interRAI-AL assessment and from the linked administrative health data.

Certain facility-level variables relevant to medication oversight were also considered for descriptive purposes. Based on previous publications from the ACCES study as well as insight from the literature, items considered for inclusion in the multivariable models included age, sex, comorbidity, number of distinct medications used, and history of health system use (hospitalizations, Emergency Department visits) in the year prior to the date of baseline assessment. The findings of the descriptive analyses were used to inform which covariates were considered for inclusion in the model.

There has been some evidence from previous publications that age greater than 90 years[112] and male sex[149,150] may be associated with risk of hospital admissions. Based on these findings, and on the importance of these variables for most outcomes in older individuals, age and sex were included as covariates in the models. As in a previous ACCES publication,[112] age was coded into the following categories: 65-79, 80-85, 86-89, and ≥90 years.

Comorbidity has been shown to be associated with hospitalization risk in previous ACCES publications,[112] as well as other studies of AL[148]and LTC [144,151] residents. In addition, comorbidity is highly associated with frailty status, and it is likely that comorbidity may be independently associated with the medication exposures of interest. Given the fact that comorbidity is a risk factor for hospitalization and is also associated with frailty status, multivariate models considering frailty as the exposure of interest (objective 2a) included adjustment for comorbidity level. Comorbidity was measured as the sum of the diagnoses documented on the interRAI-AL instrument. Consistent with previous ACCES publications,[112,120] the comorbidity score considered 49 possible diagnoses, and was coded into the following three groups: 0-3, 4-5, and ≥6 chronic conditions.

For multivariable models in which medication use was the exposure of interest (objectives 2b and 3), specific diagnoses relevant to the use of the medication class were adjusted for, rather than a measure of comorbidity. Inclusion of specific diagnoses, rather than comorbidity, allows for more direct adjustment for conditions relevant to both the medication use and the risk of hospitalization. In particular, this is relevant for insulin and oral antidiabetic agents, since only those with diabetes are eligible to use these medications. Additionally, these steps avoid the risk of masking the impact of frailty as an effect modifier, as the Full FI includes many of the same diagnoses included in the comorbidity measure. However, there was adjustment for medication number, which can be considered a proxy measure for comorbidity number, and is described in more detail below.

Previous publications from the ACCES study[112] and elsewhere[149,150,152] have identified an association between higher numbers of medications used and risk of hospitalization. There is also likely an association between use of specific medications and overall medication use. For models in which the exposure of interest was the use of certain medication classes (objectives 2b and 3), there was adjustment for 'number of medications', subtracting the medications which fall into the medication class of interest. The medication number variable was coded into the following four categories: 0-6, 7-8, 9-10, and ≥11 medications, consistent with a previous ACCES publication.[112]

Previous hospitalizations have also been identified as associated with risk of hospitalizations in AL[112] and LTC [146,150,152] residents. History of hospitalizations may also be associated with the exposure of interest, use of high-risk medications (e.g., if previous hospitalizations were due to adverse drug events, or if new medications were prescribed during the hospital stay). Thus, the multivariate models included adjustment for previous hospitalizations. History of health system

use was determined using the linked health service utilization data for the year prior to baseline assessment. As in a previous ACCES publication,[112] hospitalizations in the past year were coded into the following three groups: 0, 1 or ≥2 inpatient hospital admissions in the past year.

Additional variables which have been explored as predictors of hospitalization from DAL in previous ACCES publications were also considered as potential covariates, including marital status; strength of social relationships; fatigue; time involved in activities; and cognition and function, as determined by the interRAI Cognitive Performance Scale (CPS) and Activities of Daily Living (ADL) score. However, these variables were not included as covariates in the final multivariable models due to their importance as components of frailty measures (e.g., strength of social relationships, activity involvement, and cognition in the Full FI; function in CHESS and the Full FI; fatigue in CHSrel).

For descriptive purposes, associations between facility factors and frailty/medication use status of residents were investigated. In particular, factors related to skilled care and oversight of medication use were considered in order to explore the distribution of frailty and high-risk (HR)/antipsychotic medication use based on these measures of resident oversight. In previous ACCES studies[112,120] level of skilled staffing was represented by the presence of Licensed Practical Nurse (LPN) or Registered Nurse (RN) staff on site, and coded in the following three categories: neither on site, LPN/RN on site <24/7, and LPN/RN on site 24/7. Similarly, affiliation of a physician with the facility (especially, presence of a physician office on site) was considered, coded into the following three groups, as in a previous ACCES study:[112] no physician affiliated with site, affiliated physician with no office on site, and affiliated physician with office on site. Lastly, involvement of a pharmacist in the facility over the past month was

considered as the following three categories: no pharmacist involvement, pharmacist consultant, and pharmacist on staff.

4.4 Ethics

Ethics approval for ACCES was originally obtained from the University of Calgary Conjoint Health Research Ethics Board, the University of Alberta Research Ethics Board, and the University of Lethbridge Human Subject Research Committee. This ACCES sub-study was granted ethics approval by the University of Waterloo, Office of Research Ethics on March 16, 2015 (ORE # 20569).

4.5 Analytic Plan

All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

4.5.1 Descriptive and Bivariate Analyses

Univariate analyses were used to determine the frequency and percentage distribution of all resident (including HR and antipsychotic medication use and frailty status) and facility variables of interest among the DAL cohort. Additionally, bivariate analyses were carried out to examine: (i) the distribution of resident variables by frailty status (as determined by CHSabs, CHSrel, Full FI, Armstrong FI, and CHESS); (ii) the distribution in the use of selected HR medication classes and use of antipsychotics by DAL residents' frailty status and other characteristics; and (iii) the distribution of resident variables (including frailty and HR/antipsychotic medication use status) by outcome status over the 1-year follow-up (hospitalization, LTC admission/death, remained alive and in DAL facility). These unadjusted comparative analyses were used for identification of associations between selected independent and dependent variables of interest. Contingency tables were run to assess the association

between categorical variables, and chi-square tests were used to determine statistical significance. T-tests and analysis of variance were carried out to determine the association between continuous variables and the categorical exposure or outcome variables. No corrections were made for multiple comparisons with the bivariate analyses. The purpose of the analyses was not to draw conclusions regarding the observed associations between variables, but was rather to inform covariates to be included in multivariable models.

4.5.2 Multivariable Analysis

For the multivariable analysis, Cox proportional hazards models were utilized to estimate the importance of frailty and HR/antipsychotic medication use (individually and in combination) as predictors of first event hospitalization in the DAL cohort, controlling for possible confounders. Following a strategy used in an earlier ACCES study,[112] residents were classified into groups based on the date of their first event over the 1-year follow-up: (i) inpatient hospital admission; (ii) admission to LTC or death without prior hospital admission; (iii) other transitions without prior hospital admission; and (iv) no event and remained in DAL throughout the year. Residents were censored on the date of occurrence of LTC admission, death, or discharge to a new setting. Those who experienced none of these events and remained in a DAL facility throughout the year were censored on the date of their 1-year follow-up assessment. Possible concerns related to clustering of residents within facilities were accounted for by adjusting for facility ID in all multivariable models.

To consider the role of frailty status as an effect modifier, Cox proportional hazards models were run using four-level variables that combined measures of frailty and specified HR/antipsychotic medication use (i.e,. not frail with no use of drugs from specified medication class; frail with no use of drugs from specified class; not frail with use of 1+ drugs from

specified class; and frail with use of 1+ drugs from specified class). For the purpose of these analyses, pre-frail residents were collapsed with frail residents. Pre-frail residents would be expected to have heightened vulnerability compared to robust residents, and since frailty is used as an indicator of vulnerability in the present analyses, it was decided that it would be most reasonable to include both frail and pre-frail residents in the vulnerable category, while keeping only robust residents in the less vulnerable category. Hazard models run with medication-frailty interaction terms yielded estimates of the relative risk that a participant using certain HR/antipsychotic medications would be hospitalized (as a first event), given their frailty status. Sensitivity analyses were carried out in which pre-frail residents were collapsed with non-frail residents for the binary frailty measure. However, this approach yielded inconsistent results and findings were less clear compared to the analysis collapsing pre-frail and frail residents.

As explained above, using information from previous literature (including previous ACCES publications) and the results of the descriptive analyses, selected covariates were included in models in order to adjust for potential confounding. For frailty-hospitalization models, there was adjustment for age, sex and comorbidity, allowing for consistency in the models used for each of the key frailty measures. Inclusion of additional variables in these models may have adjusted away important components of these frailty measures, as described previously.

For models of first-event hospitalization by HR/antipsychotic medication use (with or without frailty status), there was adjustment for age, sex, specified diagnoses relevant to the medication class in question, number of distinct medications used (excluding any medications from the class of interest), and hospital admissions in the past year.

5. RESULTS

5.1 Univariate Descriptive Results

5.1.1 Baseline Resident Characteristics, Full and Linked Cohorts (Table 5.1.1)

Of the 1089 designated assisted living (DAL) residents enrolled in the Alberta Continuing Care Epidemiological Studies (ACCES) at baseline, the average age was 84.9 ± 7.3, and the majority of participants were female (76.6%) and widowed (71.4%). Residents had on average 4.6 ± 2.0 comorbid diagnoses, and were using 8.3 ± 3.7 different medications. The top 5 most common chronic conditions in descending order were dementia (57.6%), hypertension (56.5%), arthritis (53.8%), depression (34.3%) and osteoporosis (31.6%). The prevalence of mild to severe cognitive impairment (CPS score ≥2) was 59.9%, while the prevalence of limited or higher activities of daily living (ADL) impairment (ADL score ≥2) was 40.6%, suggesting a higher degree of impairment in cognitive function than physical function in DAL residents. An estimated 59.1% of residents had some degree of bladder incontinence, and 28.1% had some degree of bowel incontinence. Almost half (46.6%) of residents had little to no involvement in activities and 18.5% had weak or no meaningful social relationships. About one-fifth (19%) of residents had clinically meaningful depressive symptoms (DRS ≥ 3) and 29.2% showed moderate to very severe aggressive behaviour (ABS ≥ 1). In the previous 90 days, 28.4% of residents experienced at least one fall, and in the last year, 37.8% had at least one hospital admission. An estimated 10.4% of residents had an advance directive specifying that they did not wish to be hospitalized.

Table 5.1.1. Baseline Characteristics of DAL Residents: Full DAL Cohort (n=1,089) and Linked Cohort (n=1,066).

Resident Characteristic, n (%), unless otherwise noted	Full DAL Cohort (n=1,089)	Linked Consent Cohort (n=1,066) [§]
Sociodemographic and Social Well-being		
Age, yr		
Mean ± SD	84.9 ± 7.3	84.9 ± 7.3
65-79	272 (25.0)	268 (25.1)
80-85	285 (26.2)	280 (26.3)
86-89	247 (22.7)	243 (22.8)
≥90	285 (26.1)	275 (25.8)
Sex		
Male	254 (23.3)	248 (23.3)
Female	835 (76.7)	818 (76.7)
Marital Status		
Widowed	778 (71.4)	761 (71.4)
Married or with a partner	159 (14.6)	156 (14.6)
Never married, separated, or divorced	152 (14.0)	149 (14.0)
Strength of Social Relationships [‖]		
Moderate to high (3-5)	888 (81.5)	873 (81.9)
Low to none (0-2)	201 (18.5)	193 (18.1)
Time Involved in Activities [‡]		
Most (> 2/3 time)	158 (14.5)	157 (14.7)
Some (1/3 to 2/3 time)	424 (38.9)	417 (39.1)
Little to none (< 1/3 time)	507 (46.6)	492 (46.2)
Health and Functional Status		
Cognition (CPS score)		
Intact (0)	224 (20.6)	223 (20.9)
Borderline intact (1)	213 (19.6)	211 (19.8)
Mild impairment (2)	342 (31.4)	336 (31.5)
Moderate to severe impairment (≥ 3)	310 (28.4)	296 (27.8)
Activities of Daily Living (ADL score)		
Independent (0)	458 (42.1)	454 (42.6)
Supervision required (1)	189 (17.4)	186 (17.5)
Limited impairment (2)	134 (12.3)	126 (11.8)
Extensive assistance required or dependent (≥ 3)	308 (28.2)	300 (28.1)
Bladder Incontinence		
Continent	445 (40.9)	436 (40.9)
Some control, infrequent episodes	159 (14.6)	156 (14.6)
Occasional incontinence	118 (10.8)	114 (10.7)
Frequent episodes, no control	367 (33.7)	360 (33.8)
Bowel Incontinence		
Continent	783 (71.9)	766 (71.9)
Some control, infrequent episodes	166 (15.2)	165 (15.5)
Occasional incontinence	86 (7.9)	83 (7.8)
Frequent episodes, no control	54 (5.0)	52 (4.8)

	Full DAL Cohort (n=1,089)	Linked Consent Cohort (n=1,066) [§]
Fatigue (inability to complete ADL in past 3 days)		
None	442 (40.6)	433 (40.6)
Minimal	470 (43.2)	461 (43.3)
Moderate to Severe	177 (16.2)	172 (16.1)
Falls CAP		
None	780 (71.6)	761 (71.4)
≥1 falls/ 90 days	309 (28.4)	305 (28.6)
Depressive Symptoms (DRS score)		
No (<3)	880 (80.8)	863 (81.0)
Yes (≥3)	209 (19.2)	203 (19.0)
Aggressive Behaviour (ABS Score) [ϕ]		
None (0)	771 (70.8)	760 (71.3)
Moderate (1-2)	183 (16.8)	174 (16.3)
Severe to very severe (≥3)	135 (12.4)	132 (12.4)
No. of Chronic Conditions [Ϋ]		
Mean ± SD	4.6 ± 2.0	4.7 ± 2.0
0-3	333 (30.6)	323 (30.3)
4-5	406 (37.3)	398 (37.3)
≥6	350 (32.1)	345 (32.4)
Selected Diagnoses [¶]		
Dementia	627 (57.6)	609 (57.1)
Hypertension	615 (56.5)	604 (56.7)
Arthritis	586 (53.8)	572 (53.7)
Depression	374 (34.3)	369 (34.6)
Osteoporosis	344 (31.6)	338 (31.7)
Coronary Heart Disease	310 (29.2)	315 (29.6)
Stroke	266 (24.4)	264 (24.8)
Diabetes	246 (22.6)	243 (22.8)
Congestive Heart Failure	244 (22.4)	238 (22.3)
COPD	200 (18.4)	196 (18.4)
Anxiety	179 (16.4)	177 (16.6)
Cardiac Dysrhythmias	71 (6.5)	70 (6.6)
Lipid Abnormality	51 (4.7)	51 (4.8)
Schizophrenia	17 (1.6)	16 (1.5)
Venous Disorders	10 (0.9)	10 (0.9)
No. of Medications		
Mean ± SD	8.3 ± 3.7	8.3 ± 3.8
0-6	360 (33.1)	349 (32.7)
7-8	235 (21.6)	232 (21.8)
9-10	220 (20.2)	214 (20.1)
≥11	274 (25.1)	271 (25.4)
Advance Directive: Do Not Hospitalize		
Yes	113 (10.4)	109 (10.2)
No	976 (89.6)	957 (89.8)
No. of Inpatient Hospital Admissions in Past Year		
0	-	663 (62.2)
1	-	254 (23.8)
≥2	-	149 (14.0)

Abbreviations: DAL=Designated Assisted Living; CPS=Cognitive Performance Scale; CAP=Clinical Assessment Protocol; DRS=Depression Rating Scale; ABS=Aggressive Behaviour Scale; SD=Standard Deviation

§ Sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for

administrative data linkage.
‖ Social relationships based on a summary score of items assessing whether the resident was close to someone in the facility, had a strong or supportive relationship with the family, participated in social activities of long-standing interest, and visited or had other interactions with at least one long-standing social relation or family member in the past week.
ǂ Activity involvement reflects time when the person was awake and not receiving treatments or ADL care.
ϕ ABS: a summary scale of 4 behaviours (verbal abuse, physical abuse, socially inappropriate or disruptive, resists care), with higher scores indicating a greater number and frequency of behavioural issues
Ɏ Based on the sum of diagnoses existing out of 49 chronic conditions listed on the interRAI-AL
¶ The five most common diagnoses are listed in addition to diagnoses explored as covariates in multivariable models

5.1.2 Baseline Facility Characteristics, Full and Linked Cohorts (Table 5.1.2)

DAL residents resided in facilities with an average of 44.3 (±26.0) DAL spaces and 140.8 (±111.2) total beds. A small majority (60.5%) of residents were living in a not-for-profit or regional health authority facility and 53.9% were in a facility that was affiliated with a larger chain of AL and long-term care (LTC) facilities. Over a quarter (27.3%) of residents resided in a facility without a licensed practical nurse or registered nurse (LPN/RN) on site at any time, while 61.9% lived in a facility with an LPN and/or RN on site at all times. A minority (35.7%) of residents resided in a facility with an affiliated physician; for fewer than half of these residents (16.1% of total cohort), the affiliated physician had an office on-site. One third (33.6%) of residents were in a facility reporting no pharmacist involvement on site during the past month. Among those residing in a facility with some pharmacist input in the past month, only 4.0% (29/723) resided in a facility where the pharmacist was on staff. Approximately one half of residents (51.9%) resided in a facility within a large urban community (i.e., population one million or greater).

Table 5.1.2. Baseline Facility Characteristics: Full DAL Cohort (n=1,089) and Linked Cohort (n=1,066).

Facility Characteristic, n (%), unless otherwise noted		Full DAL Cohort (n=1,089)	Linked Consent Cohort (n=1,066)
Ownership			
	For-profit	430 (39.5)	420 (39.4)
	Not-for-profit or RHA	659 (60.5)	646 (60.6)
Part of a Chain			
	Not part of a chain or RHA-operated	159 (14.6)	157 (14.7)
	Part of AL chain only	343 (31.5)	334 (31.3)
	Part of AL & LTC chain	587 (53.9)	575 (53.9)
No. of DAL Spaces			
	Mean ± SD	44.3 ± 26.0	44.1 ± 25.9
	< 20	112 (10.3)	109 (10.2)
	20-29	173 (15.9)	172 (16.1)
	30-39	296 (27.2)	293 (27.5)
	≥ 40	508 (46.7)	492 (46.2)
Total No. of Spaces			
	Mean ± SD	140.8 ± 111.2	140.0 ± 109.7
	<55	151 (13.9)	148 (13.9)
	55-89	269 (24.7)	263 (24.7)
	90-147	263 (24.2)	259 (24.3)
	≥148	406 (37.3)	396 (37.2)
LPN/RN coverage on site			
	Neither on site	297 (27.3)	295 (27.7)
	LPN &/or RN on site <24/7	118 (10.8)	108 (10.1)
	LPN &/or RN on site 24/7	674 (61.9)	663 (62.2)
Physician (GP) Affiliated with Site			
	No	700 (64.3)	687 (64.5)
	Yes, no office on site	214 (19.7)	210 (19.7)
	Yes, office on site	175 (16.1)	169 (15.9)
Pharmacist Involved with Site/past month			
	No	366 (33.6)	354 (33.2)
	Yes, consultant	694 (63.7)	684 (64.2)
	Yes, staff	29 (2.7)	28 (2.6)
Community Size			
	<1,000	27 (2.5)	26 (2.4)
	1,000-9,999	200 (18.4)	196 (18.4)
	10,000-24,999	100 (9.2)	99 (9.3)
	25,000-999,999	197 (18.1)	193 (18.1)
	1,000,000 or more	565 (51.9)	552 (51.8)
Region			
	1 (urban)	311 (28.6)	311 (29.2)
	2 (mixed urban/rural)	234 (21.5)	228 (21.4)
	3 (rural)	155 (14.2)	153 (14.4)
	4 (urban)	281 (25.8)	268 (25.1)
	5 (rural)	108 (9.9)	106 (9.9)

Abbreviations: DAL=Designated Assisted Living; RHA=Regional Health Authority; LTC=Long Term Care; SD=Standard Deviation; LPN=Licenced Practical Nurse; RN=Registered Nurse; GP=General Practitioner

Table 5.1.3. Distribution of Medication Use among DAL Residents Overall (total cohort=1,089) and Within Drug Classes.

Drug	% Distribution of Use Among All DAL Residents (n)	% Distribution of Use Among Residents Using At Least One Drug in Drug Class
Antipsychotic Agents (1+)	**26.4 (287)***	
Atypical Antipsychotic	24.9 (271) ‖	94.4
Risperidone	11.8 (129)	45.0
Quetiapine	7.4 (81)	28.2
Olanzapine	6.2 (67)	23.3
Conventional Antipsychotic	2.3 (25)	8.7
Loxapine	0.7 (8)	2.8
Methotrimeprazine	0.6 (6)	2.1
Haloperidol	0.4 (4)	1.4
Chlorpromazine	0.2 (2)	0.7
Flupentixol	0.2 (2)	0.7
Fluphenazine	0.1 (1)	0.3
Perphenazine	0.1 (1)	0.3
Zuclopenthixol	0.1 (1)	0.3
Oral Anticoagulants (1+)	**15.2 (166)**	
Warfarin	15.1 (165)	99.4
Acenocoumarol	0.1 (1)	0.6
Oral Antiplatelet Agents (1+)	**46.3 (504)†**	
Non-ASA Oral Antiplatelet	7.2 (78)	15.5
Clopidogrel	6.5 (71)	14.1
Aminosalicylic acid, Mesalazine	0.4 (4)	0.8
Ticlopidine	0.3 (3)	0.6
ASA Oral Antiplatelet	41.3 (450)	89.3
ASA	39.1 (426)	84.5
ASA+dipyridamole	2.5 (27)	5.4
Oral Antidiabetic (1+)	**14.4 (157)‡**	
Metformin	10.3 (112)	71.3
Repaglinide	2.2 (24)	15.3
Sulfonylurea	6.2 (68)	43.3
Gliclazide	4.1 (45)	28.7
Glyburide	2.1 (23)	14.7
Thiazolidinedione	1.8 (20)	12.7
Rosiglitazone	1.7 (18)	11.5
Pioglitazone	0.2 (2)	1.27
Insulin (1+)	**5.8 (63)ϕ**	
Insulin (human): Humulin N, Novolin NPH, etc.	3.1 (34)	54.0
Insulin (human): Toronto, Novolin, Humulin R, etc.	2.3 (25)	39.7
Insulin (human): Novolin 30/70, Humulin 30/70, etc.	1.9 (21)	33.3
Insulin Unspecified	0.9 (10)	15.9
Insulin Glargine	0.2 (2)	3.2
High-Risk Drug Classes[Y]	63.3 (689)	
Use of 1 HR drug class	47.4 (516)	74.9
Use of 2+ HR drug classes	15.9 (173)	25.1

Abbreviations: DAL=Designated Assisted Living

* 9 residents were using both conventional and atypical antipsychotic agents

‖ 6 residents were using two different atypical antipsychotic agents

† 24 residents were using both ASA and non-ASA antiplatelet agents
ǂ 43 residents were using two different oral antidiabetic agents; 12 residents were using three different oral antidiabetic agents
ϕ 23 residents were using two different types of insulin; 3 residents were using three different types of insulin
Ɏ Number of HR medication classes is a measure of the number of distinct medication classes used (i.e., 1 HR medication class is any number of medications from only 1 of the 4 HR classes)
Note: 25 residents were using insulin in addition to an oral antidiabetic drug; of these, 9 residents were using insulin and sulfonylurea

5.1.3 Baseline Medication Use (Table 5.1.3 and Figure 5.1.3)

The distribution of the key medication classes and individual drugs examined among DAL residents is presented in table 5.1.3. A schematic representation of the frequency distribution of medication class exposure is shown in figure 5.1.3. More than one-quarter of residents (26.4%) were using one or more antipsychotic agents, of whom 94.4% were using atypical agents. Of the 166 residents (15.2% of sample) using oral anticoagulants, all but one resident were using warfarin, specifically. Slightly less than half (46.3%) of the sample were using one or more oral antiplatelet agents. Of this group, 89.3% were using acetylsalicylic acid (ASA)–containing oral antiplatelet agents and 15.5% were using a non-ASA oral antiplatelet agent (primarily clopidogrel). A total of 24 residents (2.2% of sample) were using both an ASA and a non-ASA antiplatelet agent. An estimated 14.4% of residents were using one or more oral antidiabetic agents and 5.8% were using one or more types of insulin. About 40% of insulin users (25/63) were also using oral antidiabetic agents. Almost two-thirds of residents (63.3%) were using at least one high-risk medication (and among this group, 25.1% were using agents from 2 or more HR drug classes).

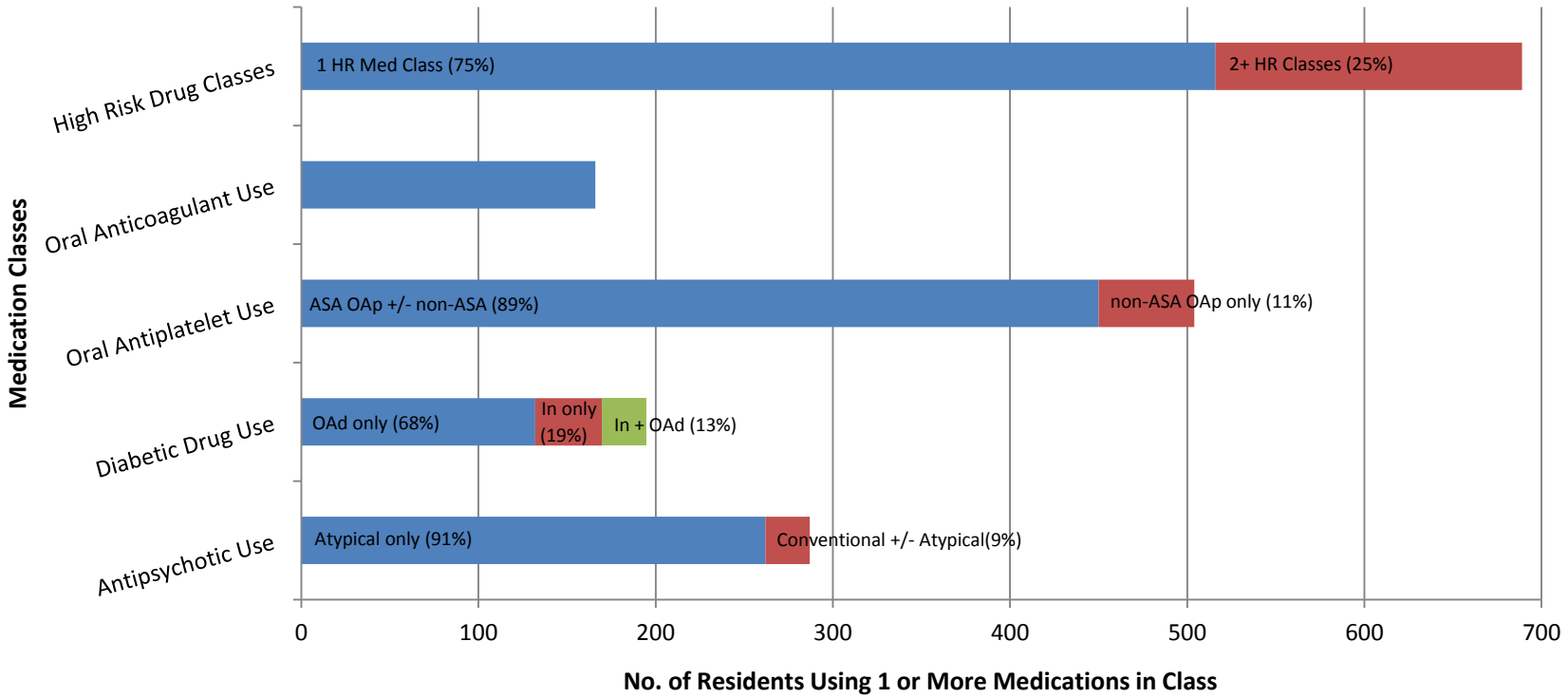


Figure 5.1.3 Distribution of High-Risk and Antipsychotic Medication Use Among DAL Residents (n=1,089**)**

Abbreviations: HR=High-rIsk; ASA=Acetylsalacylic acid; OAp=Oral Antiplatelet; OAd=Oral Antidiabetic; In=Insulin

Drug subclasses are indicated in bars along with the % distribution of use among residents using at least 1 drug in the drug class

Number of HR medication classes is a measure of the number of distinct medication classes used (i.e., 1 HR medication class is any number of medications from only 1 of the 4 HR classes)

5.1.4 Baseline Frailty Measures (Figures 5.1.4a & 5.1.4b and Table 5.1.4a & 5.14b)

The proportion of residents classified as robust, pre-frail and frail by each of the frailty measures is shown in figure 5.1.4a and detailed in table 5.1.4a. Of the 946 residents with data for the CHS frailty criteria (after value assignment using items from the interRAI-AL tool), about one-fifth (19.2%) were considered frail and slightly over half (55.0%) were considered to be pre-frail based on the CHSrel (relative cut-points) measure. Using the CHSabs (absolute cut-points) measure, almost all residents were considered either frail (48.0%) or pre-frail (48.5%). Based on the Full FI, roughly one-quarter (27.5%) of participants were found to be frail, and 38.9% were considered pre-frail. The Armstrong FI classified just over half (57.9%) of residents as frail and about one-third (32.8%) as pre-frail. Using the CHESS scale, about a quarter (24.4%) of participants were considered to be at high risk of decline (i.e., frail), and 29.4% were found to be at intermediate risk (i.e., pre-frail).

Agreement between the frailty measures in the classification of residents as frail, pre-frail, and robust is shown in table 5.1.4b. Agreement between the different frailty measures was highest between the Full FI and Armstrong FI (weighted kappa score = 0.38, 95% CI 0.35-0.41), with slightly under half (48.3%) of participants having equivalent categorizations. The lowest agreement was between CHSabs and CHESS (weighted kappa score = 0.12, CI 0.09-0.15), with 31.2% of participants assigned equivalent categorizations from the two criteria.

Overlap between classification of frail/vulnerable residents by the CHSrel, Full FI and CHESS criteria is shown in Figure 5.1.4b. Only three key measures of frailty are shown in figure 5.1.4b (CHSrel, Full FI and CHESS) as these are the three final frailty measures explored in subsequent analyses. The reasons for selection of these frailty measures include the observed distribution of frail, pre-frail and robust residents (as shown in figure 5.1.4a and table 5.1.4a), as well as the

observed associations between frailty measures and hospitalization, explained in further detail below.

Table 5.1.4a Baseline Frailty Status of DAL Residents: Full DAL Cohort and Linked Cohort.

Frailty Measure; % (n)	**Full DAL Cohort** (n=946)	**Linked Consent Cohort** (n=930) [§]
CHSabs		
Robust	3.5 (33)	3.4 (32)
Pre-frail	48.5 (459)	48.7 (453)
Frail	48.0 (454)	47.9 (445)
CHSrel		
Robust	25.8 (244)	25.8 (240)
Pre-frail	55.0 (520)	54.9 (511)
Frail	19.2 (182)	19.3 (179)
Frailty Measure; % (n)	**Full DAL Cohort** (n=1,089)	**Linked Consent Cohort** (n=1,066) [§]
Full FI		
Robust	33.6 (366)	34.2 (365)
Pre-frail	38.9 (424)	38.7 (412)
Frail	27.5 (299)	27.1 (289)
Armstrong FI		
Robust	9.4 (102)	9.5 (101)
Pre-frail	32.8 (357)	32.9 (351)
Frail	57.8 (630)	57.6 (614)
CHESS		
Robust	46.2 (503)	46.5 (496)
Pre-frail	29.4 (320)	29.3 (312)
Frail	24.4 (266)	24.2 (258)

Abbreviations: DAL=Designated Assisted Living; CHSabs= Cardiovascular Health Study Frailty Criteria (with absolute cut-points); CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale.
§ Sample excludes residents with unknown outcome who discontinued study and residents who refused consent for administrative data linkage.

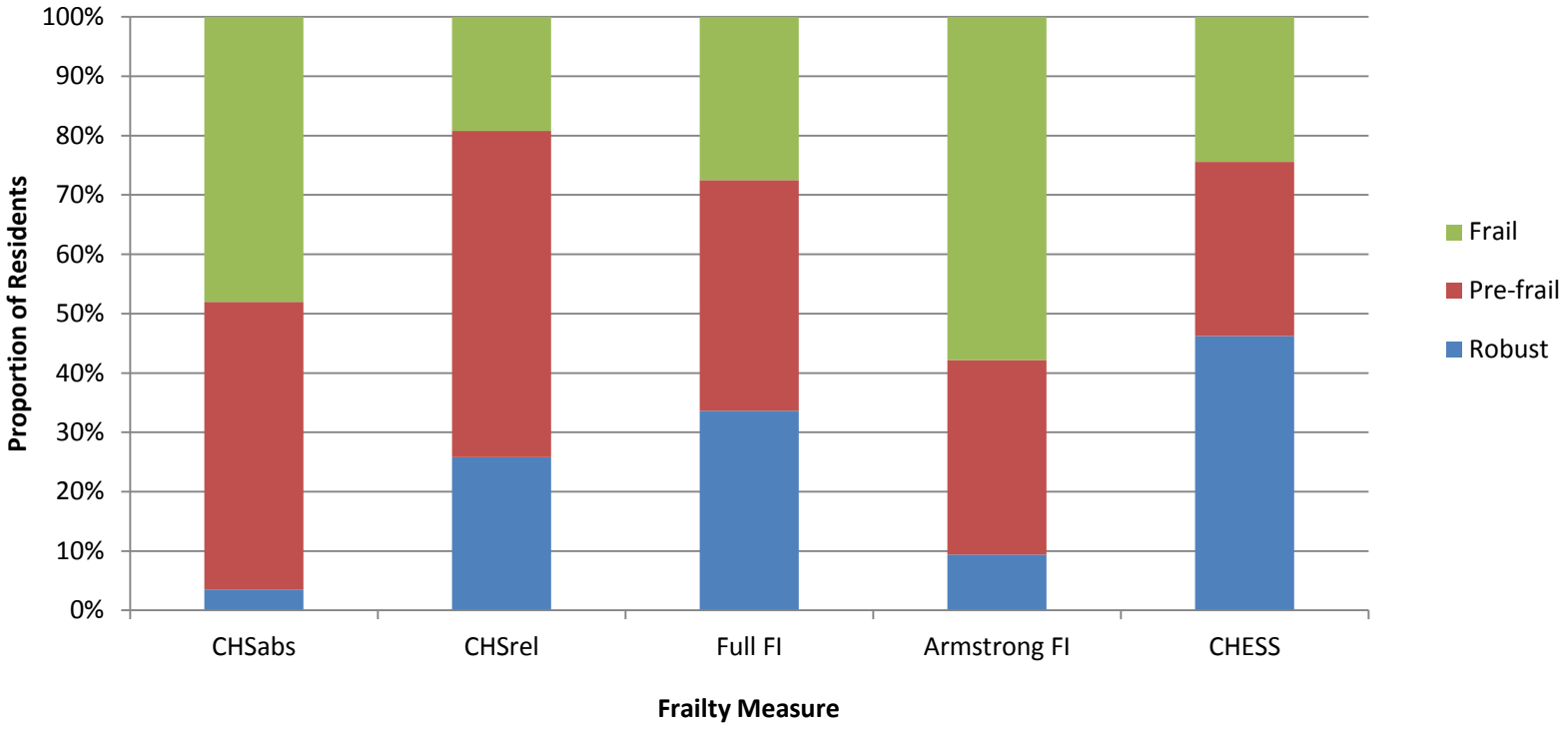


Figure 5.1.4a Proportion of DAL Residents Classified into Each Frailty Level by Frailty Measure†

Abbreviations: CHSabs=Cardiovascular Health Study Frailty Criteria (with absolute cut-points); CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; Armstrong FI=Armstrong Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale

† Based on n=1,089 for Full FI, Armstrong FI and CHESS; n=946 for CHSabs and CHSrel (missing data for CHS for 143/1,089 residents)

Table 5.1.4b. Comparison of Agreement among Frailty Measures, Full DAL Cohort (n=1089).

Comparison†	% Agreement	Weighted Kappa	95% CI
Armstrong FI – Full FI	48.3	0.38	0.35-0.41
Armstrong FI – CHSabs	56.8	0.28	0.23-0.33
Armstrong FI - CHSrel	42.9	0.22	0.18-0.26
Armstrong FI – CHESS	35.9	0.17	0.13-0.20
Full FI – CHSabs	37.0	0.17	0.13-0.20
Full FI - CHSrel	49.2	0.30	0.25-0.34
Full FI – CHESS	52.2	0.36	0.31-0.40
CHSabs – CHESS	31.2	0.12	0.09-0.15
CHSrel – CHESS	40.3	0.19	0.15-0.24

Abbreviations: CHSabs=Cardiovascular Health Study Frailty Criteria (with absolute cut-points); CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; Armstrong FI=Armstrong Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale

†All comparisons based on n=1089 residents except for comparisons involving the CHS Frailty Criteria where n=946 residents

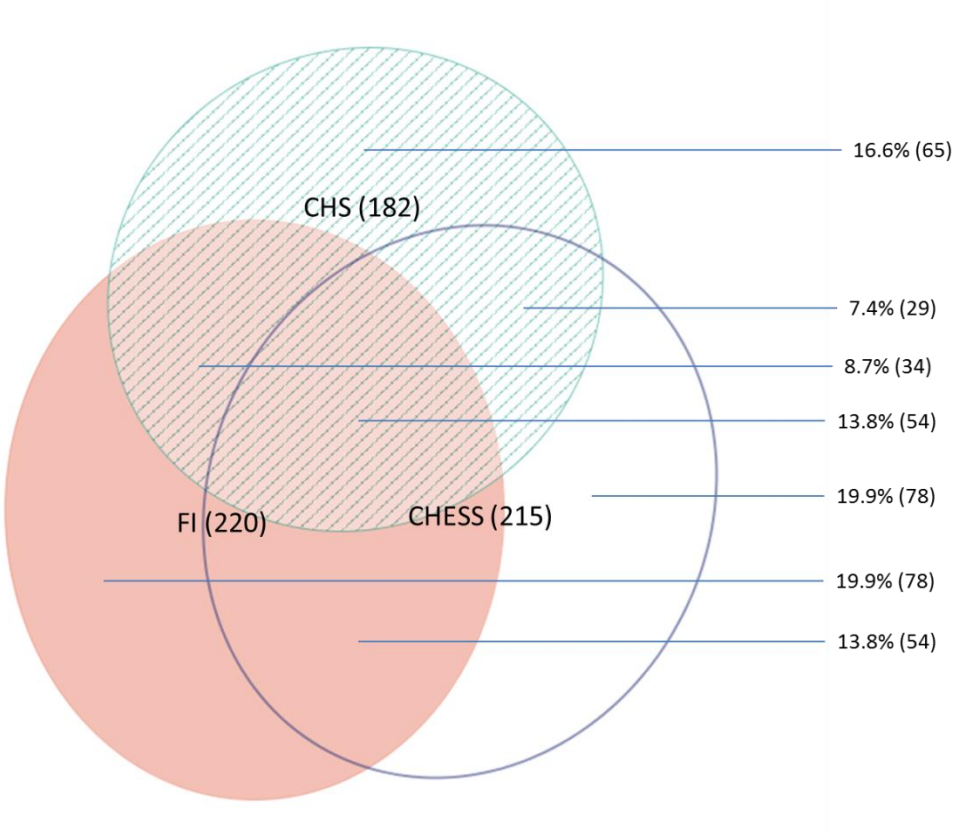


Figure 5.1.4b. Overlap Between Three Key Frailty Measures: CHSrel, Full FI and CHESS (n=946)†

*Note: Only those subjects classified as frail were included in these diagrams; pre-frail subjects were classified with non-frail (robust) subjects

†based on n=946 for all measures (common denominator based on missing data for CHS for 143/1089 subjects)

5.1.5 Outcomes

Over the 1-year follow-up period among the linked DAL cohort (n=1,066), 3.3% (n=35) of residents died without any prior hospitalization or transfer, 7.5% (n=80) were transferred to LTC as their first event, 38.7% (n=413) were admitted to an acute care hospital as their first event, 0.4% (n=4) were censored for other reasons, and 50.1% (n=534) remained in the DAL facility, without experiencing any other outcomes of interest.

5.2 Objective 1a: Examine Frailty Status (as identified by 3 measures of vulnerability) by Resident-Level Characteristics

5.2.1 Frailty and Resident-Level Characteristics (see Tables 5.2.1a – 5.2.1c)

Associations between frailty status and resident level characteristics for the three key frailty measures are shown in Tables 5.2.1a (CHSrel), 5.2.1b (Full FI) and 5.2.1c (CHESS). Mean age was found to be significantly higher in frail residents compared to pre-frail or robust residents when considering the Full FI ($F = 6.54$, p-value = 0.001) or CHSrel ($F = 5.50$, p-value = 0.004) criteria for measuring frailty. Prevalence of CHSrel frailty increased with each subsequent age group, but this finding did not reach statistical significance (p-value=0.07), whereas the prevalence of Full FI frailty was significantly higher among those aged 80 and over when compared to those aged 65-79 (p-value = 0.01). CHESS instability was not significantly associated with mean age ($F = 1.07$, p-value = 0.34) or increasing age group (p-value = 0.80). No significant associations were observed between sex and any of the frailty measures considered.

Table 5.2.1a. Baseline Characteristics of DAL Residents by Frailty Status [CHSrel]

		CHS Frailty; % of Row Total (n)			
	Total % (n)	**Not frail**	**Pre-frail**	**Frail**	**p value**
	946	25.8 (244)	55.0 (520)	19.2 (182)	
Sociodemographic and Social Well-being					
Age, yr					
Mean ± SD	84.9 ± 7.2	84.0 ± 7.6	84.8 ± 7.2	86.3 ± 7.0	0.0042
65-79	24.7 (234)	30.3 (71)	56.4 (132)	13.3 (31)	0.0687
80-85	26.4 (250)	27.2 (68)	53.2 (133)	19.6 (49)	
86-89	22.9 (217)	20.7 (45)	58.1 (126)	21.2 (46)	
≥90	25.9 (245)	24.5 (60)	52.7 (129)	22.9 (56)	
Sex					
Male	24.5 (232)	26.3 (61)	56.0 (130)	17.7 (41)	0.7845
Female	75.5 (714)	25.6 (183)	54.6 (390)	19.8 (141)	
Marital Status					
Widowed	71.4 (675)	26.7 (180)	54.8 (370)	18.5 (125)	0.6951
Married or with a partner	14.5 (137)	21.2 (29)	56.9 (78)	21.9 (30)	
Never married, separated, or divorced	14.2 (134)	26.1 (35)	53.7 (72)	20.2 (27)	
Strength of Social Relationships [ł]					
Moderate to high (3-5)	83.8 (793)	27.1 (215)	55.1 (437)	17.8 (141)	0.0126
Low to none (0-2)	16.2 (153)	19.0 (29)	54.2 (83)	26.8 (41)	
Time Involved in Activities [ǂ]					
Most (> 2/3 time)	15.8 (149)	48.3 (72)	47.0 (70)	4.7 (7)	<0.0001
Some (1/3 to 2/3 time)	40.8 (386)	29.3 (113)	56.5 (218)	14.2 (55)	
Little to none (< 1/3 time)	23.4 (411)	14.4 (59)	56.4 (232)	29.2 (120)	
Health and Functional Status					
Cognition (CPS score)					
Intact to borderline intact (0-1)	42.6 (403)	24.1 (97)	56.1 (226)	19.8 (80)	0.7357
Mild Impairment (2)	32.9 (311)	27.7 (86)	54.3 (169)	18.0 (56)	
Moderate to severe impairment (≥ 3)	24.5 (232)	26.3 (61)	53.9 (125)	19.8 (46)	
Activities of Daily Living (ADL score)					
Independent or supervision required (0-1)	62.9 (595)	34.6 (206)	53.6 (319)	11.8 (70)	<0.0001
Limited impairment (2)	11.6 (110)	21.8 (24)	60.0 (66)	18.2 (20)	
Extensive supervision required or dependent (≥ 3)	25.5 (241)	5.8 (14)	56.0 (135)	38.2 (92)	
Fatigue (inability to complete ADL in past 3 days due to diminished energy)					
None	41.7 (395)	39.5 (156)	52.9 (209)	7.6 (30)	<0.0001
Minimal	43.9 (415)	20.2 (84)	62.2 (258)	17.6 (73)	
Moderate to Severe	14.4 (136)	2.9 (4)	39.0 (53)	58.1 (79)	
Falls CAP					
None	72.0 (681)	28.5 (194)	55.6 (379)	15.9 (108)	<0.0001
≥1 falls/ 90 days	28.0 (265)	18.9 (50)	53.2 (141)	27.9 (74)	
Depressive Symptoms (DRS score)					
No (<3)	82.7 (782)	27.9 (218)	55.1 (431)	17.0 (133)	<0.0001
Yes (≥3)	17.3 (164)	15.8 (26)	54.3 (89)	29.9 (49)	
Aggressive Behaviour (ABS Score) [ϕ]					
None (0)	73.3 (693)	25.4 (176)	56.4 (391)	18.2 (126)	0.6003
Moderate (1-2)	16.8 (159)	27.7 (44)	52.2 (83)	20.1 (32)	
Severe to very severe (≥3)	9.9 (94)	25.5 (24)	48.9 (46)	25.5 (24)	

		CHS Frailty; % of Row Total (n)			
	Total % (n)	**Not frail**	**Pre-frail**	**Frail**	**p value**
	946	25.8 (244)	55.0 (520)	19.2 (182)	
No. of chronic conditions[Ɣ]					
Mean ± SD	4.6 ± 1.9	4.2 ± 1.9	4.6 ± 2.0	5.3 ± 1.9	<0.0001
0-3	30.7 (290)	34.8 (101)	56.6 (164)	8.6 (25)	<0.0001
4-5	36.7 (347)	24.2 (84)	51.9 (180)	23.9 (83)	
≥6	32.7 (309)	19.1 (59)	57.0 (176)	23.9 (74)	
No. of medications					
Mean ± SD	8.3 ± 3.6	7.9 ± 3.5	8.3 ± 3.6	9.2 ± 3.8	0.0017
0-6	32.6 (308)	29.2 (90)	54.9 (169)	15.9 (49)	0.0696
7-8	21.9 (207)	28.0 (58)	56.0 (116)	15.9 (33)	
9-10	20.4 (193)	24.4 (47)	54.4 (105)	21.2 (41)	
≥11	25.2 (238)	20.6 (49)	54.6 (130)	24.8 (59)	
No. of inpatient hospital admissions in past year (n=930)					
0	61.4 (571)	28.9 (165)	56.0 (320)	15.1 (86)	0.0003
1	24.6 (229)	23.1 (53)	52.4 (120)	24.5 (56)	
≥2	14.0 (130)	16.9 (22)	54.6 (71)	28.5 (37)	

Abbreviations: DAL=Designated Assisted Living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); CPS=Cognitive Performance Scale; CAP=Clinical Assessment Protocol; DRS=Depression Rating Scale; ABS=Aggressive Behaviour Scale; SD=Standard Deviation

ǁ Social relationships based on a summary score of items assessing whether the resident was close to someone in the facility, had a strong or supportive relationship with the family, participated in social activities of long-standing interest, and visited or had other interactions with at least one long-standing social relation or family member in the past week.

ǂ Activity involvement reflects time when the person was awake and not receiving treatments or ADL care.

ϕ ABS: a summary scale of 4 behaviours (verbal abuse, physical abuse, socially inappropriate or disruptive, resists care), with higher scores indicating a greater number and frequency of behavioural issues

Ɣ Based on the sum of diagnoses existing out of 49 chronic conditions listed on the interRAI-AL

Increasing frailty, as measured by the Full FI, was found to be significantly associated (p-value < 0.05) with limited social relationships, less time spent participating in activities, lower physical and cognitive function (ADL and CPS, respectively), higher levels of fatigue, depression, aggressive behaviour (ABS), recent falls, higher level of co-occurring chronic conditions, and higher medication number. CHESS health instability was also found to be significantly associated with all of these variables, with the exception of strength of social relationships. CHSrel frailty was found to be associated with the same variables as Full FI frailty; however, no significant associations were observed with cognitive function and aggressive behaviour, while the association with higher number of medications was less significant (p-value = 0.07). A

significant association was observed between number of hospitalizations in the past year and frailty as measured by CHSrel (p-value = 0.0003), but not by the Full FI or CHESS.

Table 5.2.1b. Baseline Characteristics of DAL Residents by Frailty Status [Full FI]

		Full FI Frailty; % of Row Total (n)			
	Total % (n)	**Not frail**	**Pre-frail**	**Frail**	**p value**
	1089	33.6 (366)	38.9 (424)	27.5 (299)	
Sociodemographic and Social Well-being					
Age, yr					
Mean ± SD	84.9 ± 7.3	84.0 ± 7.7	85.0 ± 7.4	86.0 ± 6.6	0.0015
65-79	25.0 (272)	41.2 (112)	38.6 (105)	20.2 (55)	0.0141
80-85	26.2 (285)	33.0 (94)	35.8 (102)	31.2 (89)	
86-89	22.7 (247)	28.7 (71)	42.9 (106)	28.3 (70)	
≥90	26.2 (285)	31.2 (89)	39.0 (111)	29.8 (85)	
Sex					
Male	23.3 (254)	33.5 (85)	42.1 (107)	24.4 (62)	0.3700
Female	76.7 (835)	33.7 (281)	38.0 (317)	28.4 (237)	
Marital Status					
Widowed	71.4 (778)	34.3 (267)	37.7 (293)	28.0 (218)	0.0743
Married or with a partner	14.6 (159)	27.0 (43)	40.9 (65)	32.1 (51)	
Never married, separated, or divorced	14.0 (152)	36.8 (56)	43.4 (66)	19.7 (30)	
Strength of Social Relationships [†]					
Moderate to high (3-5)	81.5 (888)	38.1 (338)	40.0 (355)	22.0 (195)	<0.0001
Low to none (0-2)	18.5 (201)	13.9 (28)	34.3 (69)	51.7 (104)	
Time Involved in Activities [‡]					
Most (> 2/3 time)	14.5 (158)	63.9 (101)	30.4 (48)	5.7 (9)	<0.0001
Some (1/3 to 2/3 time)	38.9 (424)	39.9 (169)	42.2 (179)	17.9 (76)	
Little to none (< 1/3 time)	46.6 (507)	18.9 (96)	38.9 (197)	42.2 (214)	
Health and Functional Status					
Cognition (CPS score)					
Intact to borderline intact (0-1)	40.1 (437)	52.2 (228)	39.8 (174)	8.0 (35)	<0.0001
Mild Impairment (2)	31.4 (342)	31.3 (107)	42.7 (146)	26.0 (89)	
Moderate to severe impairment (≥ 3)	28.5 (310)	10.0 (31)	33.6 (104)	56.4 (175)	
Activities of Daily Living (ADL score)					
Independent or supervision required (0-1)	59.4 (647)	50.4 (326)	39.1 (253)	10.5 (68)	<0.0001
Limited impairment (2)	12.3 (134)	15.7 (21)	46.3 (62)	38.1 (51)	
Extensive supervision required or dependent (≥ 3)	28.3 (308)	6.2 (19)	35.4 (109)	58.4 (180)	
Fatigue (inability to complete ADL in past 3 days due to diminished energy)					
None	40.6 (442)	48.4 (214)	36.4 (161)	15.2 (67)	<0.0001
Minimal	43.2 (470)	30.2 (142)	42.6 (200)	27.2 (128)	
Moderate to Severe	16.2 (177)	5.6 (10)	35.6 (63)	58.8 (104)	

	Full FI Frailty; % of Row Total (n)				
	Total % (n)	**Not frail**	**Pre-frail**	**Frail**	**p value**
	1089	33.6 (366)	38.9 (424)	27.5 (299)	
Falls CAP					
None	71.6 (780)	40.0 (312)	39.1 (305)	20.9 (163)	<0.0001
≥1 falls/ 90 days	28.4 (309)	17.5 (54)	38.5 (119)	44.0 (136)	
Depressive Symptoms (DRS score)					<0.0001
No (<3)	80.8 (880)	39.9 (351)	39.9 (351)	20.2 (178)	
Yes (≥3)	19.2 (209)	7.2 (15)	34.9 (73)	57.9 (121)	
Aggressive Behaviour (ABS Score) ϕ					
None (0)	70.8 (771)	38.8 (299)	41.0 (316)	20.2 (156)	<0.0001
Moderate (1-2)	16.8 (183)	27.9 (51)	37.2 (68)	35.0 (64)	
Severe to very severe (≥3)	12.4 (135)	11.9 (16)	29.6 (40)	58.5 (79)	
No. of chronic conditions ϒ					
Mean ± SD	4.6 ± 2.0	3.8 ± 1.6	4.8 ± 1.9	5.5 ± 2.1	<0.0001
0-3	30.6 (333)	52.9 (176)	32.7 (109)	14.4 (48)	<0.0001
4-5	37.3 (406)	32.5 (132)	40.9 (166)	26.6 (108)	
≥6	32.1 (350)	16.6 (58)	42.6 (149)	40.9 (143)	
No. of medications					
Mean ± SD	8.3 ± 3.7	7.7 ± 3.4	8.6 ± 3.9	8.7 ± 3.6	0.0002
0-6	33.1 (360)	39.7 (143)	35.6 (128)	24.7 (89)	0.0039
7-8	21.6 (235)	38.3 (90)	34.9 (82)	26.8 (63)	
9-10	20.2 (220)	28.6 (63)	41.8 (92)	29.6 (65)	
≥11	25.2 (274)	25.6 (70)	44.5 (122)	29.9 (82)	
No. of inpatient hospital admissions in past year (n=1,066)					
0	62.2 (663)	36.4 (241)	38.0 (252)	25.6 (170)	0.3622
1	23.8 (254)	31.9 (81)	38.6 (98)	29.5 (75)	
≥2	14.0 (149)	28.9 (43)	41.6 (62)	29.5 (44)	

Abbreviations: DAL=Designated Assisted Living; Full FI=Full (85-item) Frailty Index; CPS=Cognitive Performance Scale; CAP=Clinical Assessment Protocol; DRS=Depression Rating Scale; ABS=Aggressive Behaviour Scale; SD=Standard Deviation

ǁ Social relationships based on a summary score of items assessing whether the resident was close to someone in the facility, had a strong or supportive relationship with the family, participated in social activities of long-standing interest, and visited or had other interactions with at least one long-standing social relation or family member in the past week.

ǂ Activity involvement reflects time when the person was awake and not receiving treatments or ADL care.

ϕ ABS: a summary scale of 4 behaviours (verbal abuse, physical abuse, socially inappropriate or disruptive, resists care), with higher scores indicating a greater number and frequency of behavioural issues

ϒ Based on the sum of diagnoses existing out of 49 chronic conditions listed on the interRAI-AL

When considering continuous measures, mean number of comorbid diagnoses and mean medication number were each significantly higher with increasing vulnerability level in CHSrel ($F = 16.3$, p-value < 0.0001; $F = 6.4$, p-value $= 0.002$, respectively), Full FI ($F = 76.4$, p-value < 0.0001; $F = 8.6$, p-value $= 0.0002$, respectively), and CHESS ($F = 12.2$, p-value < 0.0001; $F = 8.5$, p-value $= 0.0002$, respectively).

Table 5.2.1c. Baseline Characteristics of DAL Residents by Frailty Status [CHESS]

		CHESS Frailty; % of Row Total (n)			
	Total % (n)	**Not frail**	**Pre-frail**	**Frail**	**p value**
	1089	46.2 (503)	29.4 (320)	24.4 (266)	
Sociodemographic and Social Well-being					
Age, yr					
Mean ± SD	84.9 ± 7.3	84.6 ± 7.5	84.9 ± 7.2	85.5 ± 7.1	0.3439
65-79	25.0 (272)	49.3 (134)	29.8 (81)	21.0 (57)	0.8024
80-85	26.2 (285)	43.9 (125)	30.2 (86)	26.0 (74)	
86-89	22.7 (247)	44.9 (111)	29.6 (73)	25.5 (63)	
≥90	26.2 (285)				
Sex					
Male	23.3 (254)	44.1 (112)	32.3 (82)	23.6 (60)	0.5093
Female	76.7 (835)	46.8 (391)	28.5 (238)	24.7 (206)	
Marital Status					
Widowed	71.4 (778)	47.6 (370)	28.4 (221)	24.0 (187)	0.3570
Married or with a partner	14.6 (159)	40.3 (64)	30.8 (49)	28.9 (46)	
Never married, separated, or divorced	14.0 (152)	45.4 (69)	32.9 (50)	21.7 (33)	
Strength of Social Relationships [ł]					
Moderate to high (3-5)	81.5 (888)	46.4 (412)	30.1 (267)	23.5 (209)	0.3060
Low to none (0-2)	18.5 (201)	45.3 (91)	26.4 (53)	28.4 (57)	
Time Involved in Activities [ǂ]					
Most (> 2/3 time)	14.5 (158)	53.2 (84)	31.0 (49)	15.8 (25)	<0.0001
Some (1/3 to 2/3 time)	38.9 (424)	51.9 (220)	30.4 (129)	17.7 (75)	
Little to none (< 1/3 time)	46.6 (507)	39.3 (199)	28.0 (142)	32.7 (166)	
Health and Functional Status					
Cognition (CPS score)					
Intact to borderline intact (0-1)	40.1 (437)	49.2 (215)	31.1 (136)	19.7 (86)	<0.0001
Mild Impairment (2)	31.4 (342)	50.9 (174)	28.6 (98)	20.5 (70)	
Moderate to severe impairment (≥ 3)	28.5 (310)	36.8 (114)	27.7 (86)	35.5 (110)	
Activities of Daily Living (ADL score)					
Independent or supervision required (0-1)	59.4 (647)	53.9 (349)	30.6 (198)	15.5 (100)	<0.0001
Limited impairment (2)	12.3 (134)	47.0 (63)	22.4 (30)	30.6 (41)	
Extensive supervision required or dependent (≥ 3)	28.3 (308)	29.5 (91)	29.9 (92)	40.6 (125)	
Fatigue (inability to complete ADL in past 3 days due to diminished energy)					
None	40.6 (442)	61.3 (271)	27.2 (120)	11.5 (51)	<0.0001
Minimal	43.2 (470)	41.3 (194)	33.2 (156)	25.5 (120)	
Moderate to Severe	16.2 (177)	21.5 (38)	24.9 (44)	53.7 (95)	
Falls CAP					
None	71.6 (780)	51.1 (399)	29.0 (226)	19.9 (155)	<0.0001
≥1 falls/ 90 days	28.4 (309)	33.7 (104)	30.4 (94)	35.9 (111)	
Depressive Symptoms (DRS score)					
No (<3)	80.8 (880)	49.7 (437)	29.2 (257)	21.2 (186)	<0.0001
Yes (≥3)	19.2 (209)	31.6 (66)	30.1 (63)	38.3 (80)	
Aggressive Behaviour (ABS Score) [ϕ]					
None (0)	70.8 (771)	47.5 (366)	30.5 (235)	22.0 (170)	0.0058
Moderate (1-2)	16.8 (183)	48.1 (88)	26.2 (48)	25.7 (47)	
Severe to very severe (≥3)	12.4 (135)	36.3 (49)	27.4 (37)	36.3 (49)	

	CHESS Frailty; % of Row Total (n)				
	Total % (n)	**Not frail**	**Pre-frail**	**Frail**	**p value**
	1089	46.2 (503)	29.4 (320)	24.4 (266)	
No. of chronic conditions ϒ					
Mean ± SD	4.6 ± 2.0	4.4 ± 1.9	4.6 ± 2.0	5.1 ± 1.9	<0.0001
0-3	30.6 (333)	55.3 (184)	29.4 (98)	15.3 (51)	<0.0001
4-5	37.3 (406)	43.3 (176)	30.1 (122)	26.6 (108)	
≥6	32.1 (350)				
No. of medications					
Mean ± SD	8.3 ± 3.7	7.9 ± 3.5	8.4 ± 3.6	9.0 ± 3.9	0.0002
0-6	33.1 (360)	49.4 (178)	29.7 (107)	20.8 (75)	0.0050
7-8	21.6 (235)	54.5 (128)	24.7 (58)	20.8 (49)	
9-10	20.2 (220)	41.8 (92)	30.0 (66)	28.2 (62)	
≥11	25.2 (274)	38.3 (105)	32.5 (89)	29.2 (80)	
No. of inpatient hospital admissions in past year (n=1,066)					
0	62.2 (663)	48.3 (320)	28.4 (188)	23.4 (155)	0.2382
1	23.8 (254)	46.8 (119)	28.0 (71)	25.2 (64)	
≥2	14.0 (149)	38.3 (57)	35.6 (53)	26.2 (39)	

Abbreviations: DAL=Designated Assisted Living; CHESS= Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CPS=Cognitive Performance Scale; CAP=Clinical Assessment Protocol; DRS=Depression Rating Scale; ABS=Aggressive Behaviour Scale; SD=Standard Deviation

ǁ Social relationships based on a summary score of items assessing whether the resident was close to someone in the facility, had a strong or supportive relationship with the family, participated in social activities of long-standing interest, and visited or had other interactions with at least one long-standing social relation or family member in the past week.

ǂ Activity involvement reflects time when the person was awake and not receiving treatments or ADL care.

ϕ ABS: a summary scale of 4 behaviours (verbal abuse, physical abuse, socially inappropriate or disruptive, resists care), with higher scores indicating a greater number and frequency of behavioural issues

ϒ Based on the sum of diagnoses existing out of 49 chronic conditions listed on the interRAI-AL

5.2.2 Frailty, Depression and Dementia

Each of the frailty measures was explored with depression (DRS score of 3+) and dementia (diagnosis) in order to determine the extent to which these two conditions were found to coexist with being frail within DAL residents. Venn diagrams (presented in Figure 5.2.2a) illustrate the overlap between depression, dementia and frail status defined by each of the frailty criteria. The findings from the Venn diagrams are summarized in Table 5.2.2.

The Armstrong FI, which identified the highest number of residents as frail (n = 510), also identified the highest proportion of residents as having all three conditions (10.3%), when compared to the other frailty criteria. The frailty measure that identified the smallest number of residents as frail (n = 182) was the CHSrel measure, which identified 3.4% of participants as having frailty, depression and dementia concurrently.

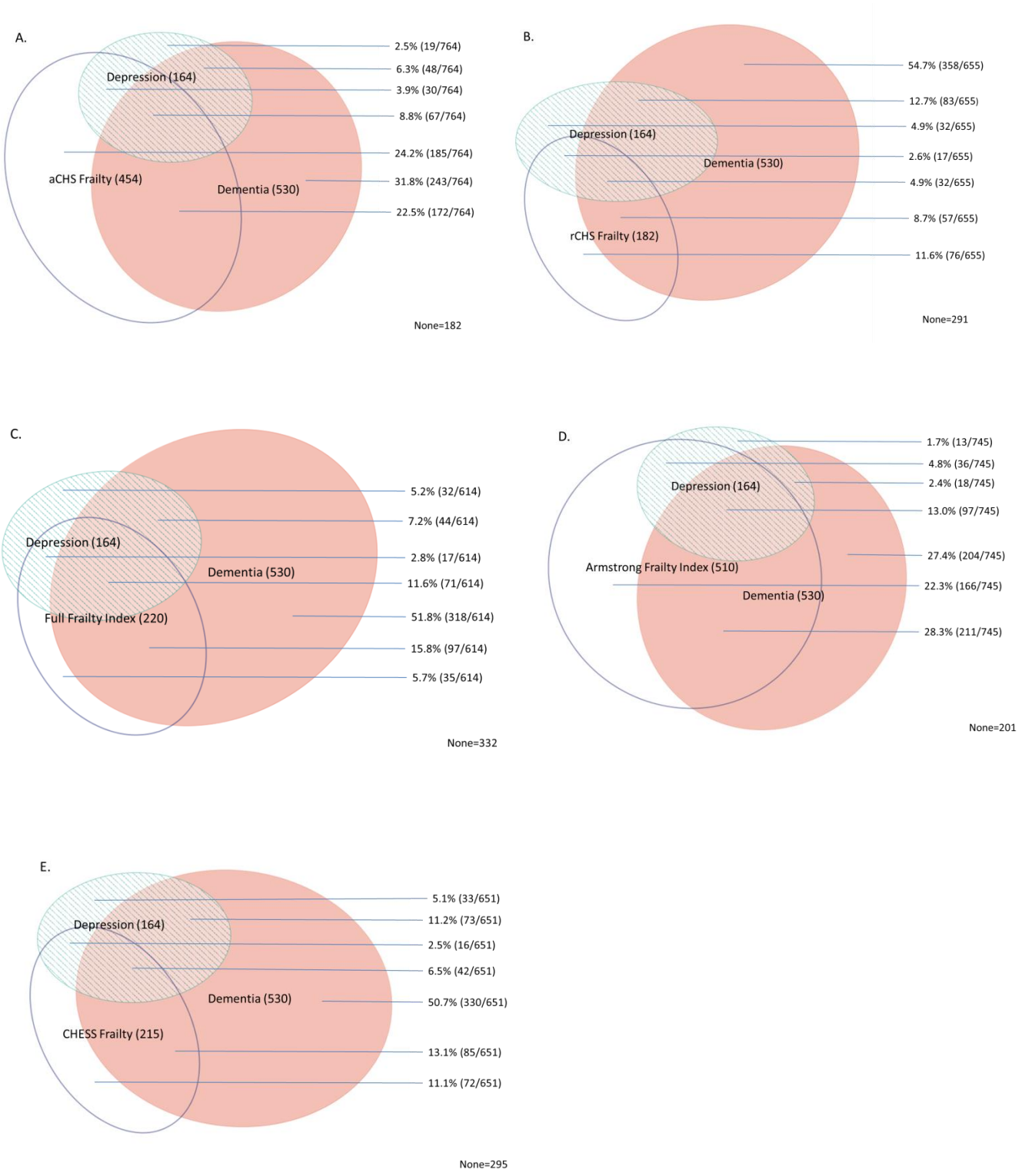


Figure 5.2.2a. Frailty,* Dementia, Depression Overlap by selected Frailty Measure Among DAL Residents (n=946)†

A. CHSabs Frailty Measure; B. CHSrel Frailty Measure; C. Full Frailty Index; D. Armstrong Frailty Index; E. CHESS Frailty

*Note: Only those subjects classified as frail were included in these diagrams; pre-frail subjects were classified with non-frail (robust) subjects

†based on n=946 for all measures (common denominator based on missing data for CHS for 143/1089 subjects)

Table 5.2.2 Frailty, Dementia, Depression Overlap by Selected Frailty Measures Among DAL Residents (n=946)†

Combinations of Frail, Dementia, Depression Characteristics	Frailty Measure*									
	CHS absolute cut-points†		CHS relative cut-points†		Full Frailty Index†		Armstrong Frailty Index†		CHESS†	
	% (n)	%§	% (n)	%§	% (n)	%§	% (n)	%§	% (n)	%§
Frail + Dementia + Depression	7.1 (67)	8.8	3.4 (32)	4.9	7.5 (71)	11.6	10.3 (97)	13.0	4.4 (42)	6.5
Frail + Dementia	18.2 (172)	22.5	6.0 (57)	8.7	10.3 (97)	15.8	22.3 (211)	28.3	9.0 (85)	13.1
Frail + Depression	3.2 (30)	3.9	1.8 (17)	2.6	1.8 (17)	2.8	3.8 (36)	4.8	1.7 (16)	2.5
Dementia + Depression	5.1 (48)	6.3	8.8 (83)	12.7	4.7 (44)	7.2	1.9 (18)	2.4	7.7 (73)	11.2
Frail only	19.6 (185)	24.2	8.0 (76)	11.6	3.7 (35)	5.7	17.6 (166)	22.3	7.6 (72)	11.1
Dementia only	25.7 (243)	31.8	37.8 (358)	54.7	33.6 (318)	51.8	21.6 (204)	27.4	34.9 (330)	50.7
Depression only	2.0 (19)	2.5	3.4 (32)	4.9	3.4 (32)	5.2	1.4 (13)	1.7	3.5 (33)	5.1
None of 3	19.2 (182)		30.8 (291)		35.1 (332)		21.3 (201)		31.2 (295)	

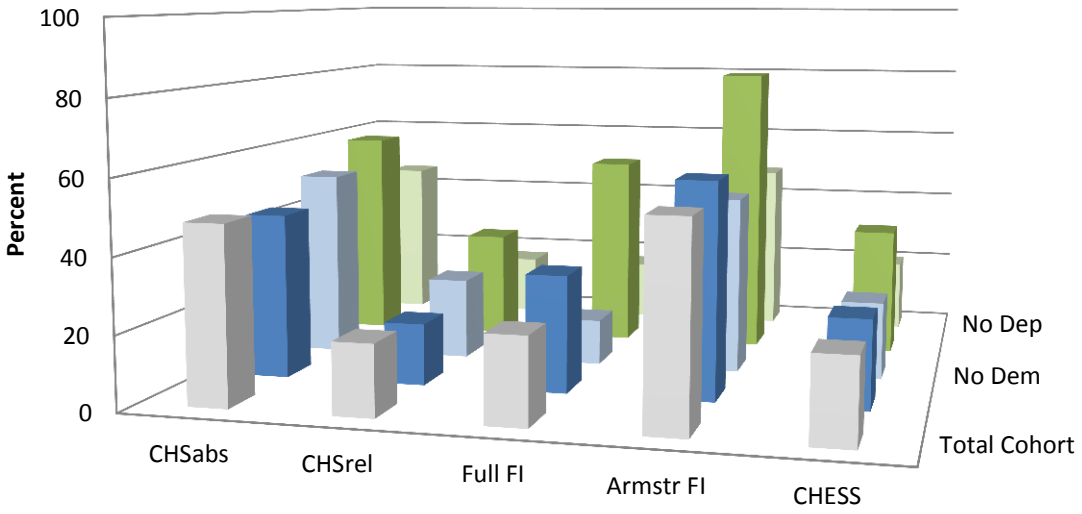
*Note: In above table, pre-frail subjects classified with non-frail (robust) subjects
†based on n=946 for all measures (common denominator based on missing data for CHS for 143/1089 subjects)
§ % distribution among those with 1 or more of the 3 characteristics

When frailty was defined by the Full FI, compared to the other frailty criteria, the smallest proportion of participants were classified as only having frailty (3.7%), and not the other two conditions. The CHSabs had the highest proportion of residents classified as only frail (19.6%), followed by the Armstrong FI (17.6%). Of the residents identified as frail by each frailty index, those identified as frail by the Full FI most frequently included residents with at least one of the other two conditions (84.1% (185/220)). When identifying frailty by the Armstrong FI or CHESS, roughly 67% of frail individuals also had dementia and/or depression (344/510; 143/215, respectively), compared to roughly 60% of frail individuals identified by either CHS measure (269/454 for CHSabs; 106/182 for CHSrel).

Figure 5.2.2b displays the proportion of those with and without dementia and depression who were identified as frail by each of the five frailty measures (the sample is restricted to the 946

residents for whom all frailty criteria could be measured). Each frailty measure identified a higher proportion of depressed residents than non-depressed residents as being frail, whereas only three of the five measures (Full FI, Armstrong FI, and CHESS) identified more residents with dementia as frail, compared to residents without dementia.

Of all of the frailty measures considered, the Armstrong FI identified the greatest proportion (81.1%) of depressed individuals as frail (133/164) and the greatest proportion of residents with dementia (58.1%) as frail (308/530). The CHSrel, in contrast, identified the lowest proportion of depressed individuals (29.9%) as frail (49/164) and the lowest proportion of residents with dementia (16.8%) as frail (89/530).



	CHSabs	CHSrel	Full FI	Armstr FI	CHESS
Total Cohort	48	19.2	23.3	53.9	22.7
Dem	45.1	16.8	31.7	58.1	24
No Dem	51.7	22.4	12.5	48.6	21.2
Dep	59.2	29.9	53.7	81.1	35.4
No Dep	45.7	17	16.9	48.2	20.1

Figure 5.2.2b. Proportion of DAL Residents identified as Frail* by selected Frailty Measure†, for Total Cohort and among those with and without Dementia or Depression

*Note: In above table, pre-frail subjects classified with non-frail (robust) subjects

†based on n=946 for all measures (common denominator based on missing data for CHS for 143/1089 subjects)

5.3 Objective 1b: Examine HR/Antipsychotic Medication Use by Resident Level Characteristics and by Frailty Status, as identified by 3 measures of vulnerability

5.3.1 HR/Antipsychotic Medication Use and Resident Characteristics

Observed associations between resident-level characteristics and use of HR medication classes are displayed in table 5.3.1a. Table 5.3.1b shows results for the association between resident-level characteristics and overall antipsychotic medication use, as well as atypical antipsychotic use, specifically. The distribution in use of each of the HR/antipsychotic medication classes by total number of medications used is shown in figure 5.3.1.

5.3.1.1 Oral Anticoagulant and Oral Antiplatelet Use (Table 5.3.1a)

Use of oral anticoagulant agents and use of oral antiplatelet agents were not significantly associated with age, but were both found to be more common in males than in females (p-value = 0.008; p-value = 0.038, respectively). Prevalence of oral anticoagulant use was higher in those who were married or were living with a partner (p-value = 0.002) (compared to widowed, never married, separated or divorced residents), whereas no significant associations were observed between oral antiplatelet use and marital status.

Neither oral anticoagulant use nor oral antiplatelet use were found to be significantly associated with strength of social relationships, time involved in activities, CPS score, ADL impairment, fatigue, DRS score, or falls in the last 90 days. Use of oral anticoagulants was significantly more prevalent in those without aggressive behaviour (p-value = 0.022) when compared to those with moderate to very severe aggressive behaviour (ABS score $\geq$1). No association was observed between ABS score and oral antiplatelet use.

Table 5.3.1a. Baseline Sociodemographic, Health and Functional Characteristics Associated with High-risk Medication Use among DAL Residents (n=1,089).

		Use of ≥1 Medications from Given Medication Class; % of Row Total (n) †			
	Total % (n)	**Oral Anticoagulants**	**Oral Antiplatelet**	**Oral Antidiabetic**	**Insulins**
	1089	15.2 (166)	46.3 (504)	14.4 (157)	5.8 (63)
Sociodemographic and Social Well-being					
Age, yr					
Mean ± SD	84.9 ± 7.3	84.7 ± 6.8	84.6 ± 7.4	83.2 ± 7.6	81.5 ± 7.1
65-79	25.0 (272)	14.3 (39)	49.3 (134)	20.6 (56)*	10.3 (28)*
80-85	26.2 (285)	17.2 (49)	42.8 (122)	13.0 (37)*	5.3 (15)*
86-89	22.7 (247)	16.2 (40)	49.4 (122)	12.6 (31)*	4.5 (11)*
≥90	26.2 (285)	13.3 (38)	44.2 (126)	11.6 (33)*	3.2 (9)*
Sex					
Male	23.3 (254)	20.5 (52)*	52.0 (132)*	20.1 (51)*	7.5 (19)
Female	76.7 (835)	13.7 (114)*	44.6 (372)*	12.7 (106)*	5.3 (44)
Marital Status					
Widowed	71.4 (778)	13.9 (108)*	45.6 (355)	13.2 (103)	5.3 (41)**
Married or with a partner	14.6 (159)	24.5 (39)*	44.7 (71)	15.7 (25)	4.4 (7)**
Never married, separated, or divorced	14.0 (152)	12.5 (19)*	51.3 (78)	19.1 (29)	9.9 (15)**
Strength Social Relationships ‖					
Moderate to high (3-5)	81.5 (888)	16.0 (142)	46.7 (415)	13.5 (120)**	5.7 (51)
Low to none (0-2)	18.5 (201)	11.9 (24)	44.3 (89)	18.4 (37)**	6.0 (12)
Time Involved in Activities ‡					
Most (> 2/3 time)	14.5 (158)	17.1 (27)	43.7 (69)	13.9 (22)	5.7 (9)
Some (1/3 to 2/3 time)	38.9 (424)	16.5 (70)	48.4 (205)	15.6 (66)	5.2 (22)
Little to none (< 1/3 time)	46.6 (507)	13.6 (69)	45.4 (230)	13.6 (69)	6.3 (32)
Health and Functional Status					
Cognition (CPS score)					
Intact to borderline intact (0-1)	40.1 (437)	16.7 (73)	48.3 (211)	18.1 (79)*	7.3 (32)
Mild impairment (2)	31.4 (342)	17.0 (58)	47.4 (162)	13.7 (47)*	4.1 (14)
Moderate to severe impairment (≥ 3)	28.5 (310)	11.3 (35)	42.3 (131)	10.0 (31)*	5.5 (17)
Activities of Daily Living (ADL score)					
Independent or supervision required (0-1)	59.4 (647)	13.9 (90)	46.7 (302)	15.0 (97)	5.4 (35)
Limited impairment (2)	12.3 (134)	14.9 (20)	49.3 (66)	12.3 (134)	9.0 (12)
Extensive supervision required or dependent (≥ 3)	28.3 (308)	18.2 (56)	44.2 (136)	28.3 (308)	5.2 (16)
Fatigue (inability to complete ADL in past 3 days)					
None	40.6 (442)	14.3 (63)	47.5 (210)	14.5 (64)	5.2 (23)
Minimal	43.2 (470)	15.3 (72)	44.9 (211)	13.4 (63)	5.1 (24)
Moderate to Severe	16.3 (177)	17.5 (31)	46.9 (83)	17.0 (30)	9.0 (16)
Falls CAP					
None	71.6 (780)	14.2 (111)	45.5 (355)	13.6 (106)	5.5 (43)
≥1 falls/ 90 days	28.4 (309)	17.8 (55)	48.2 (149)	16.5 (51)	6.5 (20)

		Use of ≥1 Medications from Given Medication Class; % of Row Total (n) †			
	Total % (n)	**Oral Anticoagulants**	**Oral Antiplatelet**	**Oral Antidiabetic**	**Insulins**
	1089	15.2 (166)	46.3 (504)	14.4 (157)	5.8 (63)
Depressive Symptoms (DRS score)					
No (<3)	80.8 (880)	15.8 (139)	46.5 (409)	15.2 (134)	6.4 (56)**
Yes (≥3)	19.2 (209)	12.9 (27)	45.5 (95)	11.0 (23)	3.4 (7)**
Aggressive Behaviour (ABS Score) ϕ					
None (0)	70.8 (771)	17.4 (134)*	46.2 (356)	14.3 (110)	6.0 (46)
Moderate (1-2)	16.8 (183)	9.3 (17)*	51.4 (94)	17.5 (32)	7.1 (13)
Severe to very severe (≥3)	12.4 (135)	11.1 (15)*	40.0 (54)	11.1 (15)	3.0 (4)
No. of chronic conditions ϒ					
Mean ± SD	4.6 ± 2.0	5.3 ± 1.8	4.8 ± 1.9	5.4 ± 2.1	5.3 ± 4.9
0-3	30.6 (333)	7.8 (26)*	40.2 (134)*	9.9 (33)*	2.1 (7)*
4-5	37.3 (406)	15.3 (62)*	50.7 (206)*	12.3 (50)*	7.1 (29)*
≥6	32.1 (350)	22.3 (78)*	46.9 (164)*	21.2 (350)*	7.7 (27)*
No. of medications					
Mean ± SD	8.3 ± 3.7	9.5 ± 3.5	9.4 ± 3.6	10.4 ± 3.8	10.7 ± 4.0
0-6	33.1 (360)	9.2 (33)*	32.5 (117)*	7.8 (28)*	2.5 (9)*
7-8	21.6 (235)	14.0 (33)*	44.7 (105)*	11.1 (26)*	4.3 (10)*
9-10	20.2 (220)	19.1 (42)*	47.7 (105)*	14.1 (31)*	6.8 (15)*
≥11	25.2 (274)	21.2 (58)*	64.6 (177)*	26.3 (72)*	10.6 (29)*
No. of inpatient hospital admissions in past year (n=1,066)					
0	62.2 (663)	12.7 (84)*	46.3 (307)	13.9 (92)	5.0 (33)
1	23.8 (254)	17.7 (45)*	42.9 (109)	13.0 (33)	6.7 (17)
≥2	14.0 (149)	23.5 (35)*	52.3 (78)	20.1 (30)	8.1 (12)

Abbreviations: DAL=Designated Assisted Living; CPS=Cognitive Performance Scale; CAP=Clinical Assessment Protocol; DRS=Depression Rating Scale; ABS=Aggressive Behaviour Scale; SD=Standard Deviation

†Row percentage values represent the percentage of residents within each category using one or more medication from the specified class

*p-value≤0.05 for the use of one or more medications from the specified class when compared to use of no medications from the specified class

**p-value≤0.10 for the use of one or more medications from the specified class when compared to use of no medications from the specified class

‖ Social relationships based on a summary score of items assessing whether the resident was close to someone in the facility, had a strong or supportive relationship with the family, participated in social activities of long-standing interest, and visited or had other interactions with at least one long-standing social relation or family member in the past week.

ǂ Activity involvement reflects time when the person was awake and not receiving treatments or ADL care.

ϕ ABS: a summary scale of 4 behaviours (verbal abuse, physical abuse, socially inappropriate or disruptive, resists care), with higher scores indicating a greater number and frequency of behavioural issues

ϒ Based on the sum of diagnoses existing out of 49 chronic conditions listed on the interRAI-AL

Prevalence of oral anticoagulant use increased with each increasing level of co-occurring morbidities (p-value < 0.0001), and prevalence of oral antiplatelet use was significantly lower among those with fewer than 4 chronic conditions, compared to those with 4 or more comorbid

diagnoses (p-value = 0.02). Oral antiplatelet use and oral anticoagulant use were both more prevalent with each increasing level of medication number (p-value < 0.0001).

Prevalence of oral anticoagulant use was significantly associated with increasing number of hospital admissions in the past year (p-value = 0.0021), whereas no significant association was observed between use of oral antiplatelet agents and previous hospitalizations.

5.3.1.2 Oral Antidiabetic and Insulin Use (Table 5.3.1a)

Use of oral antidiabetic agents was found to be significantly more prevalent in men compared to women (p-value = 0.003), while no significant association with sex was observed for the use of insulin. Use of oral antidiabetic agents and use of insulin were both more prevalent among those aged 65-79, compared with older residents (p-value = 0.01; p-value = 0.002, respectively). Oral antidiabetic use was not associated with marital status, while use of insulin was more prevalent among those never married, separated or divorced compared to married or widowed residents (p-value = 0.061).

A higher prevalence of oral antidiabetic use was observed in those without strong social relationships compared to those with moderate to high strength of social relationships (p-value=0.074). Use of oral antidiabetic agents was significantly more common in those with intact to borderline intact cognition (CPS score 0-1) compared to those with a higher level of impairment (CPS Score ≥2) (p-value = 0.007), whereas no association was observed between insulin use and CPS score. Insulin use was found to be less prevalent in those with depressive symptoms (DRS score ≥3) compared to those without (DRS score<3) (p-value=0.093), but no such association was observed for use of oral antidiabetic agents. Neither oral antidiabetic use

nor insulin use were found to be significantly associated with time involved in activities, ADL dependency, fatigue, falls in the last 90 days, ABS score, or previous hospital admissions.

Increasing prevalence of both oral antidiabetic use and insulin use were observed with each increasing level of comorbid diagnoses (p-value < 0.0001; p-value = 0.002, respectively) and medication number (p-value < 0.0001; p-value = 0.0002, respectively).

5.3.1.3 Antipsychotic Use (Table 5.3.1b)

No significant associations were observed between overall use of antipsychotics and age or sex, whereas use of atypical antipsychotic agents specifically was found to decrease with increasing age (p-value = 0.0888). For all other covariates considered, significant trends observed for atypical antipsychotic use were similar to the trends for overall antipsychotic use. Use of antipsychotic agents was found to be significantly more prevalent in those who were never married, separated or divorced compared to married or widowed residents (p-value = 0.009). Antipsychotic use was also found to be more prevalent in those lacking strong social relationships compared to those with moderate to high strength of social relationships (p-value < 0.0001) and in those with decreasing levels of active time (p-value = 0.0002).

Use of antipsychotics was significantly associated with increasing levels of cognitive impairment (CPS score) (p-value < 0.0001) and was significantly more prevalent in those requiring any level of assistance with ADLs (ADL score ≥1), compared to those who were independent in ADLs (ADL score 0) (p-value < 0.0001). Prevalence of antipsychotic use was also found to be more common in those with symptoms of depression (DRS score ≥3) compared to those without (DRS score <3) (p-value < 0.0001), and was observed to increase with each increasing level of

aggressive behaviour (ABS score) (p-value < 0.0001). Antipsychotic use was not found to be associated with fatigue or falls in the last 90 days.

Table 5.3.1b. Baseline Sociodemographic, Health and Functional Characteristics Associated with Antipsychotic Medication Use among DAL Residents (n=1,089).

		Use of ≥1 Medications from Given Medication Class/Subclass; % of Row Total (n) †	
	Total % (n)	**Overall Antipsychotic Use**	**Atypical Antipsychotic**
	1089	26.4 (287)	24.9 (271)
Sociodemographic and Social Well-being			
Age, yr			
Mean ± SD	84.9 ± 7.3	84.2 ± 7.3	84.2 ± 7.4
65-79	25.0 (272)	30.9 (84)	29.4 (80)**
80-85	26.2 (285)	27.4 (78)	26.7 (76)**
86-89	22.7 (247)	24.7 (61)	21.9 (54)**
≥90	26.2 (285)	22.5 (64)	21.4 (61)**
Sex			
Male	23.3 (254)	26.0 (66)	24.0 (61)
Female	76.7 (835)	26.5 (221)	25.2 (210)
Marital Status			
Widowed	71.4 (778)	25.3 (197)*	23.9 (186)*
Married or with a partner	14.6 (159)	22.0 (35)*	20.8 (33)*
Never married, separated, or divorced	14.0 (152)	36.2 (55)*	34.2 (52)*
Strength of Social Relationships ‖			
Moderate to high (3-5)	81.5 (888)	23.7 (210)*	22.4 (199)*
Low to none (0-2)	18.5 (201)	38.3 (77)*	35.8 (72)*
Time Involved in Activities ‡			
Most (> 2/3 time)	14.5 (158)	17.1 (27)*	15.8 (25)*
Some (1/3 to 2/3 time)	38.9 (424)	23.1 (98)*	22.2 (94)*
Little to none (< 1/3 time)	46.6 (507)	32.0 (162)*	30.0 (152)*
Health and Functional Status			
Cognition (CPS score)			
Intact to borderline intact (0-1)	40.1 (437)	14.4 (63)*	13.7 (60)*
Mild Impairment (2)	31.4 (342)	25.4 (87)*	24.0 (82)*
Moderate to severe impairment(≥ 3)	28.5 (310)	44.2 (137)*	41.6 (129)*
Activities of Daily Living (ADL score)			
Independent or supervision required (0-1)	59.4 (647)	23.3 (151)*	21.9 (142)*
Limited impairment (2)	12.3 (134)	32.1 (43)*	29.9 (40)*
Extensive supervision required or dependent (≥ 3)	28.3 (308)	30.2 (93)*	28.9 (89)*
Fatigue (inability to complete ADL in past 3 days)			
None	40.6 (442)	28.5 (126)	26.9 (119)
Minimal	43.2 (470)	23.6 (111)	21.9 (103)
Moderate to Severe	16.2 (177)	28.3 (50)	27.7 (49)
Falls CAP			
None	71.6 (780)	26.0 (203)	24.7 (193)
≥1 falls/ 90 days	28.4 (309)	27.2 (84)	25.2 (78)

		Use of ≥1 Medications from Given Medication Class/Subclass; % of Row Total (n) †	
	Total %(n)	**Overall Antipsychotic Use**	**Atypical Antipsychotic**
	1089	26.4 (287)	24.9 (271)
Depressive Symptoms (DRS score)			
No (<3)	80.8 (880)	22.6 (199)*	21.1 (186)*
Yes (≥3)	19.2 (209)	42.1 (88)*	40.7 (85)*
Aggressive Behaviour (ABS Score) ϕ			
None (0)	70.8 (771)	20.2 (156)*	18.7 (144)*
Moderate (1-2)	16.8 (183)	34.4 (63)*	33.9 (62)*
Severe to very severe (≥3)	12.4 (135)	50.4 (68)*	48.1 (65)*
No. of chronic conditions ϒ			
Mean ± SD	4.6 ± 2.0	4.7 ± 2.2	4.7 ± 2.1
0-3	30.6 (333)	30.9 (103)*	27.9 (93)**
4-5	37.3 (406)	21.7 (88)*	20.9 (85)**
≥6	32.1 (350)	27.4 (96)*	26.6 (93)**
No. of medications			
Mean ± SD	8.3 ± 3.7	8.8 ± 3.5	8.9 ± 3.5
0-6	33.1 (360)	21.4 (77)**	19.7 (71)*
7-8	21.6 (235)	27.2 (64)**	26.4 (62)*
9-10	20.2 (220)	28.6 (63)**	27.3 (60)*
≥11	25.2 (274)	30.3 (83)**	28.5 (78)*
No. of inpatient hospital admissions in past year (n=1,066)			
0	62.2 (663)	26.9 (178)*	24.9 (165)**
1	23.8 (254)	28.7 (73)*	27.6 (70)**
≥2	14.0 (149)	18.1 (27)*	18.1 (27)**

Abbreviations: CPS=Cognitive Performance Scale; CAP=Clinical Assessment Protocol; DRS=Depression Rating Scale; ABS=Aggressive Behaviour Scale

†Row percentage values represent the percentage of residents within each category using one or more medication from the specified class/subclass

*p-value≤0.05 for the use of one or more medications from the specified class when compared to use of no medications from the specified class

**p-value≤0.10 for the use of one or more medications from the specified class when compared to use of no medications from the specified class

‖ Social relationships based on a summary score of items assessing whether the resident was close to someone in the facility, had a strong or supportive relationship with the family, participated in social activities of long-standing interest, and visited or had other interactions with at least one long-standing social relation or family member in the past week.

ǂ Activity involvement reflects time when the resident was awake and not receiving treatments or ADL care.

ϕ ABS: a summary scale of 4 behaviours (verbal abuse, physical abuse, socially inappropriate or disruptive, resists care), with higher scores indicating a greater number and frequency of behavioural issues

ϒ Based on the sum of diagnoses existing out of 49 chronic conditions listed on the interRAI-AL

Use of antipsychotics was observed to be most prevalent in those with less than 3 or with more than 5 diagnoses (p-value = 0.015) when compared to those with 4 or 5 comorbid diagnoses, whereas prevalence was found to increase with each increasing level of medication number (p-value = 0.059). Prevalence of antipsychotic use was highest among those with one or zero hospital admissions in the past year, when compared to those with two or more (p-value=0.049).

Of the residents taking antipsychotic agents, 78.4% (225/287) had a dementia diagnosis, and roughly 4.9% (14/287) had a schizophrenia diagnosis. In comparison, of the residents not taking antipsychotic agents, 50.1% (402/802) had a dementia diagnosis and 0.4% (3/802) were diagnosed with schizophrenia.

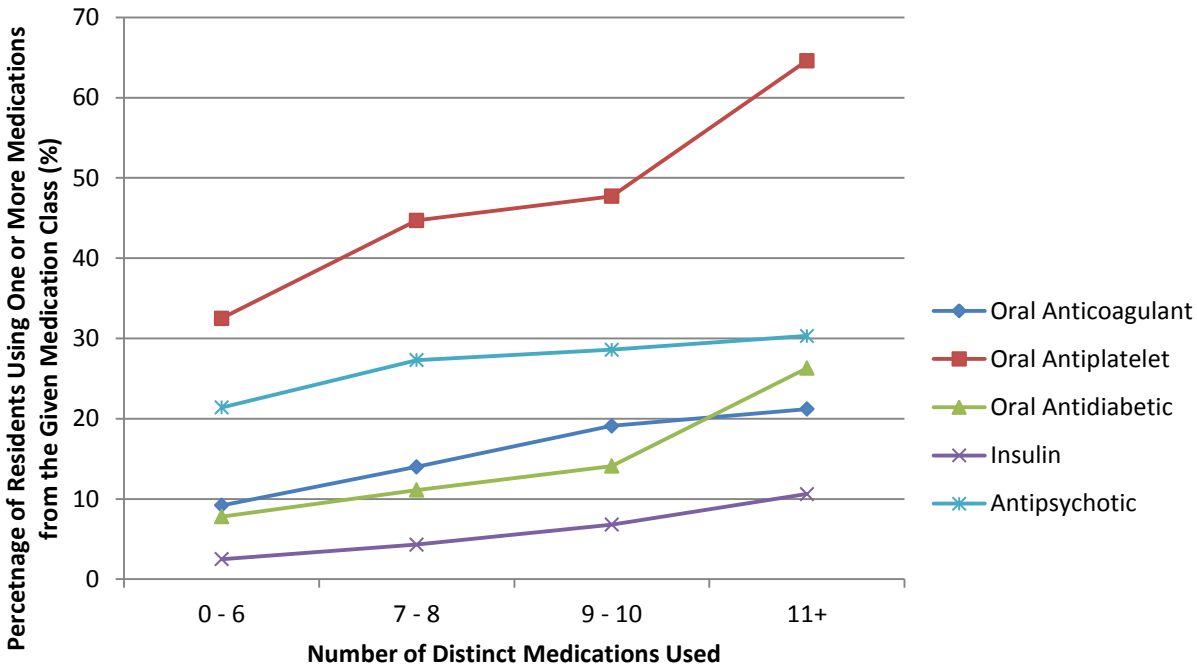


Figure 5.3.1. Distribution of HR/Antipsychotic Medication Use in Full DAL Cohort (n=1,089) by Total Medication Use Category

5.3.2 HR/Antipsychotic Medication Use and Frailty Status (Tables 5.3.2a-c)

Associations between HR/antipsychotic medication classes and frailty status, as defined by each of the three key frailty measures, are shown in table 5.3.2a (CHSrel), table 5.3.2b (Full FI) and table 5.3.2c (CHESS). No statistically significant associations were observed between the three key frailty criteria and any of the major HR medication classes of interest. Only CHSrel frailty was found to have a borderline significant (p-value = 0.069) association with oral antiplatelet use, when use of non-ASA antiplatelet agents was examined as a category distinct from use of

ASA antiplatelet agents (with or without non-ASA), compared to no use of oral antiplatelet agents. In this case CHSrel pre-frail and frail residents were found to have a lower prevalence of both non-ASA antiplatelet use and ASA antiplatelet use when compared to robust residents.

A statistically significant association of a higher prevalence of antipsychotic use was observed among those resident who were found to be frail by the Full FI, or at high risk of decline by CHESS, when compared to less vulnerable residents (p-value < 0.0001; p-value = 0.029, respectively). No significant association was observed between antipsychotic use and frailty as classified by the CHSrel criteria.

Frailty (or health instability), as determined by both the Full FI and CHESS, was also found to be significantly associated with the number of distinct medications used by residents (p-value = 0.004; p-value = 0.005, respectively), while CHSrel frailty showed a borderline significant association with medication number (p-value = 0.070).

Appendix G shows the baseline distribution of selected diagnoses (associated with use of these medication classes) and the association with frailty status, as measured by CHSrel (table a), Full FI (table b) and CHESS (table c). In all cases, the prevalence of diagnoses possibly indicating use of the drug classes of interest (Appendix G, tables a-c) was much higher than the prevalence of use of the corresponding medication classes (Tables 5.3.2a-c). Further, the selected diagnoses were found to be significantly associated with frailty status, according to the Full FI (Appendix G, table b). Examining the other measures of frailty status (CHSrel and CHESS), diagnoses associated with the use of oral anticoagulants, oral antidiabetics, combined use of insulin/oral antidiabetics, and antipsychotics (CHESS only) were found to be associated with frailty status Appendix G, tables a and c).

Table 5.3.2a. Baseline Distribution of High-risk / Antipsychotic Medication Use by Frailty Status [CHSrel Frailty Measure] among DAL Residents

	Total	CHSrel Frailty; % of column total (n)			
	% (n)	Robust	Pre-Frail	Frail	p-value
	946	25.8 (244)	55.0 (520)	19.2 (182)	
Oral Anticoagulant Use					
No anticoagulant use	84.3 (797)	88.1 (215)	83.3 (433)	81.9 (149)	0.1422
Use of 1+ anticoagulant(s)	15.8 (149)	11.9 (29)	16.7 (87)	18.1 (33)	
Oral Antiplatelet Use					
No antiplatelet use	53.3 (504)	50.4 (123)	55.2 (287)	51.7 (94)	0.4135
Use of 1+ antiplatelet(s)	46.7 (442)	49.6 (121)	44.8 (233)	48.4 (88)	
Use of non-ASA antiplatelet only	4.7 (44)	18.2 (8)	4.0 (21)	8.2 (15)	0.0691
Use of 1+ ASA (with/without non-ASA) antiplatelet(s)	42.1 (398)	46.3 (113)	40.8 (212)	40.1 (73)	
Oral Antidiabetic Use					
No oral antidiabetic use	84.3 (797)	86.5 (211)	84.6 (440)	80.2 (146)	0.2028
Use of 1+ oral antidiabetic(s)	15.8 (149)	13.5 (33)	15.4 (80)	19.8 (36)	
Insulin Use					
No insulin use	94.1 (890)	94.3 (230)	93.5 (486)	95.6 (174)	0.5680
Use of 1+ insulin(s)	5.9 (56)	5.7 (14)	6.5 (34)	4.4 (8)	
Insulin/Sulfonylurea Use					
No insulin or sulfonylurea use	88.2 (834)	88.1 (215)	87.7 (456)	89.6 (163)	0.7979
Use of insulin and/or sulfonylurea	11.8 (112)	11.9 (29)	12.3 (64)	10.4 (19)	
Any Diabetic Drug Use					
No insulin or oral antidiabetic use	80.8 (764)	82.0 (200)	81.1 (422)	78.0 (142)	0.5602
Use of insulin and/or oral antidiabetic(s)	19.2 (182)	18.0 (44)	18.9 (98)	22.0 (40)	
No. of Separate High-risk Medication Classes Used ¥					
No use of any of the 4 HR drug classes	35.5 (336)	34.4 (84)	36.9 (192)	33.0 (60)	0.4832
Use of 1 HR drug class	47.5 (449)	51.2 (125)	45.2 (235)	48.9 (89)	
Use of 2+ HR drug classes	17.0 (161)	14.3 (35)	17.9 (93)	18.1 (33)	
Antipsychotic Agents					
No antipsychotic use	75.7 (716)	75.8 (185)	76.5 (398)	73.1 (133)	0.6437
Use of 1+ antipsychotic(s)	24.3 (230)	24.2 (59)	23.5 (122)	26.9 (49)	
No. of Medications					
0-6	32.6 (308)	36.9 (90)	32.5 (169)	26.9 (49)	0.0696
7 or 8	21.9 (207)	23.8 (58)	22.3 (116)	18.1 (33)	
9 or 10	20.4 (193)	19.3 (47)	20.2 (105)	22.5 (41)	
≥11	25.2 (238)	20.1 (49)	25.0 (130)	32.4 (59)	

Abbreviations: DAL=Designated Assisted Living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points)
¥ The High-Risk Medication Classes variable is a measure of the number of distinct medication classes used (i.e. 1 HR medication class is any number of medications from only 1 of the 4 HR classes)

Table 5.3.2b. Baseline Distribution of High-risk / Antipsychotic Medication Use by Frailty Status [Full FI Frailty Measure] among DAL Residents

	Total	Full FI Frailty; % of column total (n)			
	% (n)	Robust	Pre-Frail	Frail	p-value
Overall	1089	33.6 (366)	38.9 (424)	27.5 (299)	
Oral Anticoagulant Use					
No anticoagulant use	84.8 (923)	86.9 (318)	84.7 (359)	82.3 (246)	0.2577
Use of 1+ anticoagulant(s)	15.2 (166)	13.1 (48)	15.3 (65)	17.7 (53)	
Oral Antiplatelet Use					
No antiplatelet use	53.7 (585)	56.3 (206)	51.4 (218)	53.9 (161)	0.3914
Use of 1+ antiplatelet(s)	46.3 (504)	43.7 (160)	48.6 (206)	46.1 (138)	
Use of non-ASA antiplatelet only	5.0 (54)	3.5 (13)	5.4 (23)	6.0 (18)	0.4393
Use of 1+ ASA (with/without non-ASA) antiplatelet(s)	41.3 (450)	40.2 (147)	43.2 (183)	40.1 (120)	
Oral Antidiabetic Use					
No oral antidiabetic use	85.6 (932)	83.9 (307)	86.3 (366)	86.6 (259)	0.5196
Use of 1+ oral antidiabetic(s)	14.4 (157)	16.1 (59)	13.7 (58)	13.4 (40)	
Insulin Use					
No insulin use	94.2 (1026)	95.9 (351)	92.4 (392)	94.6 (283)	0.1092
Use of 1+ insulin(s)	5.8 (63)	4.1 (15)	7.5 (32)	5.4 (16)	
Insulin/Sulfonylurea Use					
No insulin or sulfonylurea use	88.8 (967)	89.9 (329)	87.7 (372)	89.0 (266)	0.6287
Use of insulin and/or sulfonylurea	11.2 (122)	10.1 (37)	12.3 (52)	11.0 (33)	
Any Diabetic Drug Use					
No insulin or oral antidiabetic use	82.1 (894)	81.7 (299)	81.6 (346)	83.3 (249)	0.8211
Use of insulin and/or oral antidiabetic(s)	17.9 (195)	18.3 (67)	18.4 (78)	16.7 (50)	
No. of Separate High-risk Medication Classes Used ¥					
No use of any of the 4 HR drug classes	36.7 (400)	39.3 (144)	35.6 (151)	35.1 (105)	0.5807
Use of 1 HR drug class	47.4 (516)	45.6 (167)	46.9 (199)	50.2 (150)	
Use of 2+ HR drug classes	15.9 (173)	15.0 (55)	17.5 (74)	14.7 (44)	
Antipsychotic Agents					
No antipsychotic use	73.6 (802)	82.0 (300)	76.6 (325)	59.2 (177)	<0.0001
Use of 1+ antipsychotic(s)	26.4 (287)	18.0 (66)	23.4 (99)	40.8 (122)	
No. of Medications					
0-6	33.1 (360)	39.1 (143)	30.2 (128)	29.8 (89)	0.0039
7 or 8	21.6 (235)	24.6 (90)	19.3 (82)	21.2 (63)	
9 or 10	20.2 (220)	17.2 (63)	21.7 (92)	21.7 (65)	
≥11	25.2 (274)	19.1 (70)	28.8 (122)	27.4 (82)	

Abbreviations: DAL=Designated Assisted Living; Full FI= Full (86-item) Frailty Index

¥ The High-Risk Medication Classes variable is a measure of the number of distinct medication classes used (i.e. 1 HR medication class is any number of medications from only 1 of the 4 HR classes)

Table 5.3.2c. Baseline Distribution of High-risk / Antipsychotic Medication Use by Frailty Status [CHESS Health Instability Measure] among DAL Residents

	Total	CHESS Frailty; % of column total (n)			
	% (n)	Robust	Pre-Frail	Frail	p-value
	1089	46.2 (503)	29.4 (320)	24.4 (266)	
Oral Anticoagulant Use					
No anticoagulant use	84.8 (923)	85.5 (430)	85.3 (273)	82.7 (23.8)	0.5629
Use of 1+ anticoagulant(s)	15.2 (166)	14.5 (73)	14.7 (47)	17.3 (46)	
Oral Antiplatelet Use					
No antiplatelet use	53.7 (585)	54.3 (273)	53.7 (172)	52.6 (140)	0.9098
Use of 1+ antiplatelet(s)	46.3 (504)	45.7 (230)	46.3 (148)	47.4 (126)	
Use of non-ASA antiplatelet only	5.0 (54)	4.2 (21)	5.0 (16)	6.4 (17)	0.7676
Use of 1+ ASA (with/without non-ASA) antiplatelet(s)	41.3 (450)	41.5 (209)	41.3 (132)	41.0 (109)	
Oral Antidiabetic Use					
No oral antidiabetic use	85.6 (932)	85.1 (428)	86.9 (278)	85.0 (226)	0.7352
Use of 1+ oral antidiabetic(s)	14.4 (157)	47.8 (75)	13.1 (42)	15.0 (40)	
Insulin Use					
No insulin use	94.2 (1026)	94.0 (473)	94.1 (301)	94.7 (252)	0.9157
Use of 1+ insulin(s)	5.8 (63)	6.0 (30)	5.9 (19)	5.3 (14)	
Insulin/Sulfonylurea Use					
No insulin or sulfonylurea use	88.8 (967)	88.9 (447)	89.7 (287)	87.6 (233)	0.7245
Use of insulin and/or sulfonylurea	11.2 (122)	11.1 (56)	10.3 (33)	12.4 (33)	
Any Diabetic Drug Use					
No insulin or oral antidiabetic use	82.1 (894)	82.1 (413)	82.5 (264)	81.6 (217)	0.9589
Use of insulin and/or oral antidiabetic(s)	17.9 (195)	17.9 (90)	17.5 (56)	18.4 (49)	
No. of Separate High-risk Medication Classes Used ¥					
No use of any of the 4 HR drug classes	36.7 (400)	38.2 (192)	36.6 (117)	34.2 (91)	0.7311
Use of 1 HR drug class	47.4 (516)	45.3 (228)	48.8 (156)	49.6 (132)	
Use of 2+ HR drug classes	15.9 (173)	16.5 (83)	14.7 (47)	16.2 (43)	
Antipsychotic Agents					
No antipsychotic use	73.6 (802)	73.6 (370)	78.1 (250)	68.4 (182)	0.0294
Use of 1+ antipsychotic(s)	26.4 (287)	26.4 (133)	21.9 (70)	31.6 (84)	
No. of Medications					
0-6	33.1 (360)	35.4 (178)	33.4 (107)	28.2 (75)	0.0050
7 or 8	21.6 (235)	25.4 (128)	18.1 (58)	18.4 (49)	
9 or 10	20.2 (220)	18.3 (92)	20.6 (66)	23.3 (62)	
≥11	25.2 (274)	20.9 (105)	27.8 (89)	30.1 (80)	

Abbreviations: DAL=Designated Assisted Living; CHESS= Changes in Health, End-stage disease and Signs and Symptoms of medical problems scale

¥ The High-Risk Medication Classes variable is a measure of the number of distinct medication classes used (i.e. 1 HR medication class is any number of medications from only 1 of the 4 HR classes)

5.4 Objective 2a: Examine Association between Frailty Status and First Event Hospitalization during a 1-year follow-up

5.4.1 Bivariate Analysis: Resident-level Covariates and Outcome (Table 5.4.1)

In order to gain insight into covariates relevant to the outcome of interest, chi-square analyses were conducted using resident-level correlates found to be associated with hospitalization in the literature and previous ACCES publications (see Table 5.4.1). Increased rates of first-event hospitalization were found to be significantly associated (p-value < 0.05) with decreased strength of social relationships, less time spent engaged in activities, lower levels of cognitive impairment, ADL scores greater than 2 (compared to ADL of 2 or lower), greater fatigue, fewer depressive symptoms, more chronic conditions, a higher number of medications, and a higher number of hospital admissions in the past year. There were also marginally significant associations (p-value < 0.1) observed between increased hospitalization and two resident-level variables of interest: one or more falls in the past 90 days, and lower levels of aggressive behaviour.

Table 5.4.1. Distribution of First Event Outcome by Baseline Sociodemographic, Health and Functional Characteristics among DAL Residents

		Outcome; % of row total (n) †			
	Total* % (n)	**Hospital**	**LTC or death**	**Still in DAL**	**p value**
	1066	38.9 (413)	10.8 (115)	50.3 (534)	
Age, yr					
Mean ± SD	84.9 ± 7.3	85.2 ± 7.1	86.1 ± 6.5	84.4 ± 7.5	
65-79	25.1 (268)	36.6 (97)	8.3 (22)	55.1 (146)	0.3925
80-85	26.3 (280)	39.4 (110)	10.0 (28)	50.5 (141)	
86-89	22.8 (243)	37.9 (92)	13.2 (32)	49.0 (119)	
≥90	25.8 (275)	41.5 (114)	12.0 (33)	46.5 (275)	
Sex					
Male	23.3 (248)	41.1 (101)	11.8 (29)	47.2 (116)	0.5266
Female	76.7 (818)	38.2 (312)	10.5 (86)	51.2 (418)	
Marital Status					
Widowed	71.4 (761)	38.7 (293)	10.8 (82)	50.5 (383)	0.7711
Married or with a partner	14. 6 (156)	40.4 (63)	12.8 (20)	46.8 (73)	
Never married, separated, or divorced	14.0 (149)	38.5 (57)	8.8 (13)	52.7 (78)	
Strength of Social Relationships ‡					
Moderate to high (3-5)	81.9 (873)	38.2 (332)	9.5 (83)	52.3 (455)	0.0026
Low to none (0-2)	18.1 (193)	42.2 (81)	16.7 (32)	41.1 (79)	
Time Involved in Activities ‡					
Most (> 2/3 time)	14.7 (157)	34.8 (54)	5.8 (9)	59.4 (92)	0.0002
Some (1/3 to 2/3 time)	39.1 (417)	39.6 (165)	7.7 (32)	52.8 (220)	
Little to none (< 1/3 time)	46.2 (492)	39.6 (194)	15.1 (74)	45.3 (222)	
Cognition (CPS score)					
Intact to borderline intact (0-1)	40.7 (434)	41.8 (180)	5.3 (23)	52.9 (228)	<0.0001
Mild Impairment (2)	31.5 (336)	39.1 (131)	9.3 (31)	51.6 (173)	
Moderate to severe impairment (≥ 3)	27.8 (296)	34.5 (102)	20.6 (61)	44.9 (133)	
Activities of Daily Living (ADL score)					
Independent or supervision required (0-1)	60.1 (640)	37.8 (241)	6.1 (39)	56.0 (357)	<0.0001
Limited impairment (2)	11.8 (126)	33.3 (42)	16.7 (21)	50.0 (63)	
Extensive supervision required or dependent (≥ 3)	28.1 (300)	43.5 (130)	18.4 (55)	38.1 (114)	
Fatigue (inability to complete ADL in past 3 days)					
None	40.6 (433)	34.2 (147)	8.6 (37)	57.2 (246)	<0.0001
Minimal	43.3 (461)	39.4 (181)	10.0 (46)	50.6 (233)	
Moderate to Severe	16.1 (172)	49.4 (85)	18.6 (32)	32.0 (55)	
Falls CAP					
None	71.4 (761)	37.5 (284)	10.0 (76)	52.5 (398)	0.0622
≥1 falls/ 90 days	28.6 (305)	42.4 (129)	12.8 (39)	44.7 (136)	
Depressive Symptoms (DRS score)					
No (<3)	81.0 (863)	39.3 (338)	9.3 (80)	51.4 (442)	0.0040
Yes (≥3)	19.0 (203)	37.1 (75)	17.3 (35)	45.5 (92)	

		Outcome; % of row total (n) †			
	Total* % (n)	**Hospital**	**LTC or death**	**Still in DAL**	**p value**
	1066	38.9 (413)	10.8 (115)	50.3 (534)	
Aggressive Behaviour (ABS score) ϕ					
None (0)	71.3 (760)	40.2 (305)	9.1 (69)	50.7 (384)	0.0649
Moderate (1-2)	16.3 (174)	37.8 (65)	13.4 (23)	48.8 (84)	
Severe to very severe (≥3)	12.4 (132)	32.6 (43)	17.4 (23)	50.0 (66)	
No. of chronic conditions Ɣ					
Mean ± SD	4.7 ± 2.0	4.8 ± 2.0	4.9 ± 2.1	4.4 ± 1.9	
0-3	30.3 (323)	33.2 (107)	9.3 (30)	57.5 (185)	0.0195
4-5	37.3 (398)	39.0 (155)	11.3 (45)	49.6 (197)	
≥6	32.4 (345)	44.0 (151)	11.7 (40)	44.3 (152)	
No. of medications					
Mean ± SD	8.3 ± 3.8	9.1 ± 3.8	8.5 ± 3.6	7.7 ± 3.4	
0-6	32.7 (349)	30.5 (106)	10.3 (36)	59.2 (206)	0.0002
7-8	21.8 (232)	37.9 (88)	13.4 (31)	48.7 (113)	
9-10	20.1 (214)	41.0 (87)	9.4 (20)	49.5 (105)	
≥11	25.4 (271)	48.9 (132)	10.4 (28)	40.7 (110)	
No. of inpatient hospital admissions in past year					
0	62.2 (663)	34.5 (228)	11.3 (75)	54.2 (358)	<0.0001
1	23.8 (254)	39.7 (100)	9.1 (23)	51.2 (129)	
≥2	14.0 (149)	57.1 (85)	11.4 (17)	31.5 (47)	

Abbreviations: LTC=Long Term Care; DAL=designated assisted living; CPS=Cognitive Performance Scale; CAP=Clinical Assessment Protocol; DRS=Depression Rating Scale; ABS=Aggressive Behaviour Scale

* Sample excludes 3 residents with unknown outcome who discontinued the study and 20 who refused linkage consent for administrative data.

† Four residents (0.4% of the cohort) had other outcomes (censored at date of first discharge from DAL) and were omitted from the comparisons.

ǁ Social relationships based on a summary score of items assessing whether the resident was close to someone in the facility, had a strong or supportive relationship with the family, participated in social activities of long-standing interest, and visited or had other interactions with at least one long-standing social relation or family member in the past week.

ǂ Activity involvement reflects time when the person was awake and not receiving treatments or ADL care.

ϕ The ABS is a summary scale of 4 behaviours (verbal abuse, physical abuse, socially inappropriate or disruptive, resists care), with higher scores indicating a greater number and frequency of behavioural issues

Ɣ Based on the sum of diagnoses existing out of 49 chronic conditions listed on the interRAI-AL

5.4.2 Bivariate Analyses: Frailty and Outcome (Table 5.4.2)

Preliminary chi-square analyses revealed that all of the vulnerability measures considered (four frailty measures [CHSabs, CHSrel, Full FI, and Armstrong FI] and one health instability measure [CHESS]) along with a single clinical item (fatigue, i.e., ability to complete ADLs over past 3 days) were each significantly associated (p-value < 0.0001) with the categorical first-event outcome variable (hospitalization; transfer to LTC or death; and remaining in DAL) over a 1-year follow-up. The results of the analyses are shown in table 5.4.2. In general, as vulnerability level increased for any of the measures considered, rates of first-event hospitalization and transfer to LTC or death were observed to increase, while the proportion of residents remaining in DAL decreased. Exceptions were (1) the association between hospitalization and both CHSabs and Armstrong FI, where pre-frail residents had the lowest rate of first-event hospitalization, and (2) the association between hospitalization and Full FI, where pre-frail residents had the highest rate of first-event hospitalization.

Table 5.4.2. Distribution of First Event Outcome by Baseline Frailty Status among DAL Residents

		Outcome; % of row total (n)†			
	Total* % (n)	**Hospital**	**LTC or death**	**Still in DAL**	**p value**
	1066	38.7 (413)	10.8 (115)	50.1 (534)	
Frailty Measure					
CHSabs (n=930)					
Robust	3.4 (32)	37.5 (12)	3.1 (1)	59.4 (19)	<0.0001
Pre-frail	48.7 (453)	31.9 (144)	7.1 (32)	61.0 (275)	
Frail	47.9 (445)	47.3 (210)	13.5 (60)	39.2 (174)	
CHSrel (n=930)					
Robust	25.8 (240)	31.0 (74)	6.7 (16)	62.3 (149)	<0.0001
Pre-frail	55.0 (511)	39.6 (202)	8.4 (43)	52.0 (265)	
Frail	19.2 (179)	50.6 (90)	19.1 (34)	30.3 (54)	
Full FI					
Robust	34.2 (365)	32.5 (118)	3.3 (12)	64.2 (233)	<0.0001
Pre-frail	38.7 (412)	45.5 (187)	10.0 (41)	44.5 (183)	
Frail	27.1 (289)	37.5 (108)	21.5 (62)	41.0 (118)	
Armstrong FI					
Robust	9.5 (101)	37.0 (37)	3.0 (3)	60.0 (60)	<0.0001
Pre-frail	32.9 (351)	33.7 (118)	5.1 (18)	61.1 (214)	
Frail	57.6 (614)	42.2 (258)	15.4 (94)	42.5 (260)	
CHESS					
Low risk	46.5 (496)	33.5 (165)	8.1 (40)	58.4 (288)	<0.0001
Intermediate risk	29.3 (312)	43.9 (137)	9.9 (31)	46.2 (144)	
High-risk	24.2 (258)	43.2 (111)	17.1 (44)	39.7 (102)	
Fatigue (past 3 days) ϕ					
None	40.6 (433)	34.2 (147)	8.6 (37)	57.2 (246)	<0.0001
Minimal	43.3 (461)	39.4 (181)	10.0 (46)	50.7 (233)	
Moderate to severe	16.1 (172)	49.4 (85)	18.6 (32)	32.0 (55)	

Abbreviations: LTC=Long Term Care; DAL=designated assisted living; CHSabs= Cardiovascular Health Study Frailty Criteria (with absolute cut-points); CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; ADL=Activities of Daily Living

* Sample excludes 3 residents with unknown outcome who discontinued the study and 20 who refused consent for linkage of administrative data.

† Four residents (0.4% of the cohort) had other outcomes (censored at date of first discharge from DAL) and were omitted from the comparisons.

ϕ Fatigue is defined by the interRAI-AL as inability to complete normal day-to-day activities (e.g. ADLs, IADLs) in last 3 days, due to diminished energy

5.4.3 Cox Proportional Hazards Models: Frailty and Hospitalization (Table 5.4.3.)

The six frailty and vulnerability measures were examined in unadjusted and adjusted Cox proportional hazards regression models to determine associations between measures of vulnerability and time to first event hospitalization over a 1-year follow-up (Table 5.4.3). Adjusted models included age, sex and comorbidity level, and all models were adjusted for

clustering by facility. Significant associations were observed in unadjusted and adjusted models when considering the CHSrel, Full FI and CHESS measures, as well as fatigue. However, no statistically significant associations were observed between CHSabs or Armstrong FI frailty measures and first event hospitalization in either unadjusted or adjusted analyses.

Table 5.4.3. Unadjusted and adjusted hazard ratios[§] (95% CIs) for hospitalization during 1 year follow-up associated with selected frailty measures, DAL Residents (n=1,066).

	HR (95% CI)	
	Unadjusted	**Adjusted[†]**
Frailty Measure		
CHS Absolute (n=930)		
Robust (reference)	1.00	1.00
Pre-frail	0.80 (0.46-1.40)	0.77 (0.44-1.33)
Frail	1.47 (0.87-2.48)	1.32 (0.78-2.24)
CHS Relative (n=930)		
Robust (reference)	1.00	1.00
Pre-frail	**1.43 (1.07-1.91)**	**1.37 (1.02-1.83)**
Frail	**2.30 (1.69-3.13)**	**2.11 (1.53-2.92)**
Full Frailty Index (n=1066)		
Robust (reference)	1.00	1.00
Pre-frail	**1.63 (1.23-2.08)**	**1.51 (1.19-1.92)**
Frail	**1.50 (1.14-1.99)**	**1.33 (1.02-1.75)**
Armstrong Frailty Index (n=1066)		
Robust (reference)	1.00	1.00
Pre-frail	0.90 (0.62-1.29)	0.85 (0.59-1.24)
Frail	1.34 (0.93-1.94)	1.17 (0.80-1.71)
CHESS Health Instability (n=1066)		
Low Risk (0) (reference)	1.00	1.00
Intermediate Risk (1-2)	**1.44 (1.16-1.80)**	**1.40 (1.13-1.73)**
High Risk (≥3)	**1.63 (1.27-2.10)**	**1.53 (1.18-1.99)**
Fatigue, past 3 days (n=1066) [ϕ]		
None (0) (reference)	1.00	1.00
Minimal (1)	**1.25 (1.01-1.55)**	1.17 (0.94-1.45)
Moderate to Severe (≥2)	**1.99 (1.50-2.62)**	**1.81 (1.37-2.40)**

Abbreviations: DAL=designated assisted living; CHS=Cardiovascular Health Study Frailty Criteria; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate p<0.05.
†Adjusted for age, sex and comorbidity level (sum of 49 possible diagnoses recorded on the interRAI-AL)
ϕ Fatigue is defined by the interRAI-AL as inability to complete normal day-to-day activities (e.g. ADLs, IADLs) in last 3 days, due to diminished energy

CHSrel frailty was most highly associated with time to first event hospitalization when compared to the other measures of vulnerability. The risk of first event hospitalization was 1.37 (95% CI 1.02-1.83) times higher for CHSrel pre-frail residents and 2.11 (95% CI 1.53-2.92) times higher for frail, when compared to robust residents in adjusted analyses. The Full FI showed a higher risk of first event hospitalization for pre-frail residents (HR=1.51, 95% CI 1.19-1.92) than for frail residents (HR=1.33, 95% CI 1.02-1.75) when compared to robust residents. Those at intermediate risk according to CHESS had a hazard ratio for first event hospitalization of 1.40 (95% CI 1.13-1.73) while those at high risk had a hazard ratio of 1.53 (95% CI 1.18-1.99), when compared to low risk participants. After adjustment, residents with minimal fatigue did not have a significantly greater risk of first event hospitalization than those without fatigue; however, those with moderate to severe fatigue were 1.81 (95% CI 1.37-2.40) times more likely to be hospitalized as a first event, compared to residents without fatigue.

5.5 Objective 2b: Examine Association between Exposure to High-Risk and Antipsychotic Medication Measures and First Event Hospitalization during a 1-year follow-up

5.5.1 Bivariate Analyses: High-Risk/Antipsychotic Medication Exposure and Outcome (Table 5.5.1)

Chi-square analyses examining the association between use of relevant medication classes and first-event outcomes of interest are shown in table 5.5.1. No significant association was observed between first-event outcome and use of oral anticoagulants or overall use of oral antiplatelets. However, significantly higher rates of hospitalization and lower rates of death/LTC transfer, and remaining in DAL were observed among residents using only non-ASA antiplatelet agents when compared to those not using any antiplatelet agents, or those using ASA antiplatelet agents (with or without non-ASA).

Insulin use was not found to be significantly associated with first-event outcome, and oral antidiabetic use was borderline significant (p-value = 0.095). However, two measures combining insulin use with oral antidiabetic use (insulin and/or sulfonylurea use; and any diabetic drug use) were both found to be significantly associated with first-event outcome, with higher rates of hospitalization and death/transfer to LTC as a first-event (and lower rates of remaining in DAL over 1-year follow-up) among those using the medications of interest when compared to those not using these medications.

The rate of 1-year first-event hospitalization was found to be significantly higher for those residents who used medications from one of the HR drug classes of interest, and increased further for those using medications from 2 or more of the HR drug classes of interest, when compared to residents using no medications from any of the four HR classes (p-value = 0.038).

Prevalence of antipsychotic use had a marginally significant association with first-event outcome (p-value=0.084) with rates of death/transfer to LTC higher (and hospitalization or remaining in DAL lower) among antipsychotic users, compared to those not using antipsychotic agents.

Rates of first-event hospitalization were observed to increase with increasing number of distinct medications used by residents, while rates of remaining in DAL over the 1-year follow-up were generally found to decrease (p-value = 0.0002).

Table 5.5.1. Distribution of First Event Outcome by Baseline High-risk and Antipsychotic Medication Use among DAL Residents

		Outcome; % of row total (n) †			
	Total* % (n)	**Hospital**	**LTC or death**	**Still in DAL**	**p value**
	1066	38.7 (413)	10.8 (115)	50.1 (534)	
Oral Anticoagulant Use					
No anticoagulant use	84.6 (902)	37.8 (339)	11.0 (99)	51.2 (460)	0.2049
Use of 1+ anticoagulant(s)	15.4 (164)	45.1 (74)	9.8 (16)	45.1 (74)	
Oral Antiplatelet Use					
No antiplatelet use	53.7 (572)	36.7 (209)	11.2 (64)	52.1 (297)	0.2785
Use of 1+ antiplatelet(s)	46.3 (494)	41.5 (204)	10.4 (51)	48.2 (237)	
Use of non-ASA antiplatelet only	5.0 (53)	58.5 (31)	9.4 (5)	32.1 (17)	0.0389
Use of 1+ ASA (with/without non-ASA antiplatelet(s)	41.3 (441)	39.4 (173)	10.5 (46)	50.1 (220)	
Oral Antidiabetic Use					
No oral antidiabetic use	85.5 (911)	37.8 (343)	10.6 (96)	51.7 (469)	0.0948
Use of 1+ oral antidiabetic(s)	14.5 (155)	45.5 (70)	12.3 (19)	42.2 (65)	
Insulin Use					
No insulin use	94.2 (1004)	38.6 (386)	10.6 (106)	50.8 (508)	0.3488
Use of 1+ insulin(s)	5.8 (62)	43.6 (27)	14.5 (9)	41.9 (26)	
Insulin/Sulfonylurea Use					
No insulin or sulfonylurea use	88.6 (945)	38.2 (359)	10.2 (96)	51.6 (486)	0.0272
Use of insulin and/or sulfonylurea	11.4 (121)	44.6 (54)	15.7 (19)	39.7 (48)	
Any Diabetic Drug Use					
No insulin or oral antidiabetic use	82.0 (874)	37.3 (325)	10.6 (92)	52.1 (454)	0.0355
Use of insulin and/or oral antidiabetic(s)	18.0 (192)	46.1 (88)	12.0 (23)	41.9 (80)	
No. of Separate High-risk Medication Classes Used ¥					
No use of any of the 4 HR drug classes	36.5 (389)	33.9 (131)	10.3 (40)	55.8 (216)	0.0377
Use of 1 HR drug class	47.6 (507)	40.1 (203)	11.5 (58)	48.4 (245)	
Use of 2+ HR drug classes	15.9 (170)	46.7 (79)	10.1 (17)	43.2 (73)	
Antipsychotic Use					
No antipsychotic use	73.9 (788)	39.5 (310)	9.6 (75)	50.9 (399)	0.0839
Use of 1+ antipsychotic(s)	26.1 (278)	37.1 (103)	14.4 (40)	48.6 (135)	
No. of medications					
0-6	32.7 (349)	30.5 (106)	10.3 (36)	59.2 (206)	0.0002
7 or 8	21.8 (232)	37.9 (88)	13.4 (31)	48.7 (113)	
9 or 10	20.1 (214)	41.0 (87)	9.4 (20)	49.5 (105)	
≥11	25.4 (271)	48.9 (132)	10.4 (28)	40.7 (110)	

Abbreviations: LTC=Long Term Care; DAL=designated assisted living

* Sample excludes 3 residents with unknown outcome who discontinued the study and 20 who refused consent for linkage of administrative data.

† Four residents (0.4% of the cohort) had other outcomes (censored at date of first discharge from DAL) and were omitted from the comparisons.

¥ Number of HR medication classes is a measure of the number of distinct high-risk medication classes used (i.e. 1 HR medication class is any number of medications from only 1 of the 4 HR classes)

5.5.2 Cox Proportional Hazards Models: High-Risk and Antipsychotic Medication Use and Hospitalization (Table 5.5.2)

In age- and sex-adjusted models, many high-risk medication variables of interest were found to be significantly associated with time to first-event hospitalization, including use of one or more oral anticoagulants, oral antiplatelet agents, and oral antidiabetic agents, as well as both measures of combined insulin/oral antidiabetic use (insulin and/or sulfonylurea use, and any diabetic drug use). Additionally, in age- and sex-adjusted models, a dose-response relationship was observed between the number of distinct high-risk drug classes used and risk of first-event hospitalization. In general, these associations were no longer statistically significant in models with higher levels of adjustment for potential confounders, including selected diagnoses (some of which represented underlying indications for receiving the selected drugs of interest), number of hospitalizations in the past year, and number of distinct drugs used (excluding the drug(s) of interest).

Table 5.5.2. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1 year follow-up associated with selected drug measures, DAL Residents (n=1,066).

	Model A[†] HR (95% CI)	**Model B[†] HR (95% CI)**	**Model C[†] HR (95% CI)**	**Model D[†] HR (95% CI)**
	N=1,066	N=1,066	N=1,066	N=1,066
Oral Anticoagulant Use [Φ] *Reference: no anticoagulant use*				
Use of 1+ anticoagulant(s) (n=164)	**1.31 (1.02-1.68)**	1.15 (0.91-1.47)	1.11 (0.87-1.42)	1.14 (0.89-1.45)
Oral Antiplatelet Use [¶] *Reference: no antiplatelet use*				
Use of 1+ antiplatelet(s) (n=494)	**1.20 (1.00-1.44)**	1.15 (0.97-1.36)	1.16 (0.98-1.37)[‖]	1.13 (0.96-1.33)
Use of non-ASA antiplatelet only (n=53)	**2.02 (1.28-3.19)**	**2.02 (1.32-3.08)**	**1.90 (1.26-2.86)**	**1.79 (1.23-2.59)**
Use of 1+ ASA (with/without non-ASA) antiplatelet(s) (n=441)	1.12 (0.93-1.33)	1.07 (0.91-1.27)	1.09 (0.92-1.28)	1.07 (0.91-1.26)
Oral Antidiabetic Use [Ɣ] *Reference: no oral antidiabetic use*				
Use of 1+ oral antidiabetic(s) (n=155)	**1.35 (1.10-1.65)**	1.04 (0.71-1.53)	1.12 (0.76-1.66)	1.12 (0.75-1.66)
Insulin Use [ǁ] *Reference: no insulin use*				
Use of 1+ insulin(s) (n=62)	1.36 (0.89-2.09)	1.03 (0.66-1.63)	0.99 (0.63-1.55)	1.03 (0.65-1.63)
Insulin/Sulfonylurea Use [Ɣǁ] *Reference: no insulin or sulfonylurea use*				
Use of insulin and/or sulfonylurea (n=121)	**1.36 (1.05-1.78)**	1.10 (0.76-1.60)	1.09 (0.76-1.57)	1.12 (0.77-1.64)
Any Diabetic Drug Use [¥ǁ] *Reference: no insulin or oral antidiabetic use*				
Use of insulin and/or oral antidiabetic(s) (n=192)	**1.44 (1.18-1.75)**	1.30 (0.85-2.00)	1.38 (0.93-2.06)	1.33 (0.88-2.02)
# High-Risk (HR) Drug Classes [Φ ¶ Ɣ ǁ] *Reference: no use of any of the 4 HR drug classes*				
Use of 1 HR drug class (n=507)	**1.28 (1.01-1.63)**	1.24 (0.97-1.59)[‖]	1.26 (0.98-1.61)[‖]	1.21 (0.95-1.53)
Use of 2+ HR drug classes (n=170)	**1.69 (1.25-2.29)**	1.42 (0.98-2.04)[‖]	1.39 (0.97-1.99)[‖]	1.31 (0.92-1.86)
Antipsychotic Drug Use * *Reference: no antipsychotic use*				
Use of 1+ antipsychotic(s) (n=278)	0.98 (0.75-1.28)	1.05 (0.79-1.39)	1.08 (0.81-1.45)	1.09 (0.82-1.44)

Abbreviations: DAL=designated assisted living; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate $p \leq 0.05$; ‖ $p < 0.10$.

† Model A: adjusted for age and sex only; Model B adjusted for age, sex, selected diagnoses (see tables 5.6.1a-5.6.1i); Model C adjusted for age, sex, selected diagnoses (see tables 5.6.1a-5.6.1i), # hospitalizations/past year; Model D: adjusted for age, sex, selected diagnoses, # hospitalizations/past year, # drugs (excluding drug(s) of interest).
ϕ Models B-D selected diagnoses adjusted for included stroke, coronary heart disease, congestive heart failure, cardiac dysrhythmias, venous disorders (deep vein thrombosis, chronic venous insufficiency, pulmonary embolism, superficial venous thrombosis or phlebitis, varicose veins).
¶ Models B-D selected diagnoses adjusted for included stroke, hypertension, coronary heart disease, diabetes, lipid abnormality.
Ɏ Models B-D selected diagnoses adjusted for included diabetes, congestive heart failure, lipid abnormality, hypertension, coronary heart disease.
‖ Models B-D selected diagnoses adjusted for included diabetes, congestive heart failure, hypertension, chronic obstructive pulmonary disease
* Models B-D selected diagnoses adjusted for included dementia, schizophrenia, anxiety, depression.
Note: Comparable estimates were observed for all models based on sample size n=930 (sample available for Cardiovascular Health Study Frailty Criteria analyses).

When considering the subclass of oral antiplatelet agents used, use of ASA antiplatelet agents (with or without additional use of non-ASA antiplatelets) was not significantly associated with an increased risk of hospitalization in age- and sex-adjusted models. Use of non-ASA antiplatelet agents (largely clopidogrel), however, was found to be associated with a two-fold risk of first-event hospitalization when compared to residents not using oral antiplatelet agents. The statistically significant relationship between non-ASA antiplatelet use and hospitalization persisted in models with greater adjustment for potential confounders (including age, sex, selected diagnoses (stroke, hypertension, coronary heart disease, diabetes, lipid abnormality), number of hospitalizations in past year, and number of medications (excluding antiplatelet agents)), with a hazard ratio of 1.79 (95% CI 1.23-2.59) in the most fully adjusted model.

Use of antipsychotic agents was not found to be associated with an increased risk of first-event hospitalization in age- and sex-adjusted models, or in any of the more fully adjusted models.

5.6 Objective 3: Determine whether Frailty Measures act to modify the Associations between specific High-Risk Medication use and Hospitalization during the 1-year Follow-up.

5.6.1 Cox Proportional Hazards Models: High-Risk and Antipsychotic Medication Use, Frailty and Hospitalization

Using Cox proportional hazards models, categorical measures capturing an interaction between the selected frailty measure and medication class of interest were analyzed to explore potential effect modification of the medication – hospitalization association by frailty measure. In these initial analyses, the reference group was composed of non-frail residents not exposed to the medication measure/class of interest. The categorical frailty-medication measures were analysed in several models, adjusting for potential confounders. Model A included adjustment for age and sex only; model B included adjustment for age, sex and selected diagnoses; model C included adjustment for age, sex, selected diagnoses and number of hospitalizations in the past year, and model D included adjustment for all factors in model C, in addition to the total number of medications used by the resident (excluding medications from the class of interest).

The findings from the analyses are shown in tables 5.6.1a – 5.6.1i. For all medication variables considered, the age- and sex-adjusted model (model A) revealed that frail individuals (both those using the medication of interest, and those not using the medication), had a significantly increased risk of first-event hospitalization when compared to non-frail individuals not using the medication of interest, regardless of the frailty measure used. For the majority of medication variables in the model A analyses, the risk was highest among frail individuals using the medication of interest (with the exception of antipsychotic use in CHESS frail residents).

In some cases, when CHESS was used to classify frailty, use of the medications of interest in non-frail residents was associated with significantly elevated risk of hospitalization (when

compared to non-frail individuals not using the drug of interest). However, in all cases but three (i.e., use of non-ASA antiplatelet agents, use of any diabetes medication, and use of 2 or more high-risk drugs), this risk was no longer significant upon further adjustment. When considering model A for antipsychotic use, residents using antipsychotic agents who were robust according to the Full FI were at a significantly decreased risk of hospitalization compared to non-frail non-antipsychotic users, but this observation was no longer significant after further adjustment.

Table 5.6.1a. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with anticoagulant drug – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	**Full FI Adj HR (95% CI)**	**CHESS Adj HR (95% CI)**
	N=930	N=1066	N=1066
Model A Adjusted for age, sex only			
Not frail - no anticoagulant use	1.00	1.00	1.00
Not frail – use of 1+ anticoagulant(s)	1.15 (0.61-2.17)	1.02 (0.61-1.72)	**1.43 (1.01-2.03)**
Frail – no anticoagulant use	**1.57 (1.14-2.17)**	**1.50 (1.13-1.98)**	**1.56 (1.28-1.90)**
Frail – use of 1+ anticoagulant(s)	**2.03 (1.39-2.98)**	**2.08 (1.44-3.00)**	**1.88 (1.38-2.56)**
Model B[†] Adjusted for age, sex, selected diagnoses			
Not frail – no anticoagulant use	1.00	1.00	1.00
Not frail – use of 1+ anticoagulant(s)	1.13 (0.56-2.26)	0.95 (0.56-1.59)	1.31 (0.93-1.85)
Frail – no anticoagulant use	**1.50 (1.08-2.08)**	**1.41 (1.07-1.85)**	**1.47 (1.20-1.80)**
Frail – use of 1+ anticoagulant(s)	**1.78 (1.21-2.60)**	**1.74 (1.22-2.47)**	**1.56 (1.12-2.15)**
Model C[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year			
Not frail – no anticoagulant use	1.00	1.00	1.00
Not frail – use of 1+ anticoagulant(s)	1.03 (0.51-2.08)	1.01 (0.59-1.72)	1.35 (0.94-1.93)
Frail – no anticoagulant use	**1.46 (1.04-2.04)**	**1.44 (1.09-1.89)**	**1.48 (1.21-1.82)**
Frail – use of 1+ anticoagulant(s)	**1.64 (1.10-2.45)**	**1.64 (1.13-2.39)**	**1.45 (1.04-2.02)**
Model D[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year, # drugs[‡]			
Not frail – no anticoagulant use	1.00	1.00	1.00
Not frail – use of 1+ anticoagulant(s)	1.02 (0.50-2.09)	1.00 (0.59-1.69)	1.37 (0.96-1.96)
Frail – no anticoagulant use	**1.43 (1.02-2.00)**	**1.37 (1.05-1.79)**	**1.43 (1.17-1.75)**
Frail – use of 1+ anticoagulant(s)	**1.64 (1.09-2.47)**	**1.63 (1.12-2.36)**	**1.44 (1.03-2.01)**

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index, CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate p<0.05.
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models B-D: selected diagnoses adjusted for included stroke, coronary heart disease, congestive heart failure, cardiac dysrhythmias, venous disorders (deep vein thrombosis, chronic venous insufficiency, pulmonary embolism, superficial venous thrombosis or phlebitis, varicose veins);
‡drug number excludes use of anticoagulant(s)

Table 5.6.1b. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with oral antiplatelet – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	**Full FI Adj HR (95% CI)**	**CHESS Adj HR (95% CI)**
	n=930	N=1066	N=1066
Model A Adjusted for age, sex only			
Not frail - no oral antiplatelet use	1.00	1.00	1.00
Not frail – use of 1+ oral antiplatelet(s)	1.25 (0.81-1.93)	0.93 (0.66-1.31)	1.27 (0.95-1.70)
Frail – no oral antiplatelet use	**1.67 (1.23-2.27)**	**1.34 (1.04-1.71)**	**1.59 (1.20-2.11)**
Frail – use of 1+ oral antiplatelet(s)	**2.00 (1.45-2.75)**	**1.76 (1.28-2.42)**	**1.83 (1.41-2.39)**
Model B[†] Adjusted for age, sex, selected diagnoses			
Not frail – no oral antiplatelet use	1.00	1.00	1.00
Not frail – use of 1+ oral antiplatelet(s)	1.22 (0.77-1.91)	0.90 (0.64-1.27)	1.23 (0.90-1.66)
Frail – no oral antiplatelet use	**1.63 (1.18-2.26)**	**1.30 (1.01-1.67)**	**1.54 (1.16-2.06)**
Frail – use of 1+ oral antiplatelet(s)	**1.84 (1.32-2.57)**	**1.65 (1.23-2.23)**	**1.70 (1.31-2.22)**
Model C[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year			
Not frail – no oral antiplatelet use	1.00	1.00	1.00
Not frail – use of 1+ oral antiplatelet(s)	1.24 (0.79-1.96)	0.94 (0.68-1.31)	1.24 (0.93-1.65)
Frail – no oral antiplatelet use	**1.60 (1.13-2.25)**	**1.32 (1.03-1.70)**	**1.51 (1.12-2.04)**
Frail – use of 1+ oral antiplatelet(s)	**1.80 (1.28-2.54)**	**1.67 (1.25-2.23)**	**1.69 (1.30-2.21)**
Model D[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year, # drugs[‡]			
Not frail – no oral antiplatelet use	1.00	1.00	1.00
Not frail – use of 1+ oral antiplatelet(s)	1.28 (0.81-2.02)	0.95 (0.68-1.33)	1.22 (0.91-1.64)
Frail – no oral antiplatelet use	**1.60 (1.12-2.28)**	**1.31 (1.01-1.68)**	**1.47 (1.11-1.96)**
Frail – use of 1+ oral antiplatelet(s)	**1.76 (1.24-2.48)**	**1.58 (1.20-2.09)**	**1.59 (1.24-2.06)**

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate p<0.05.
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models B-D: selected diagnoses adjusted for included stroke, hypertension, coronary heart disease, diabetes, lipid abnormality.
‡drug number excludes use of antiplatelet(s)

In more fully adjusted models, the highest risk most often remained among frail individuals using the drug of interest, when compared to non-frail individuals who were not using the drug. However, in some cases, the risk was no longer statistically significant (i.e. CHSrel frailty and CHESS frailty with oral antidiabetic use, or with insulin/sulfonylurea use; any measure of frailty with insulin use) in the fully adjusted model (Model D). In all cases but one (CHSrel frailty with antipsychotic use), frail individuals who were not using the drug of interest were still at a significant risk for first-event hospitalization compared to non-frail individuals not using the drug of interest in the fully adjusted model.

Table 5.6.1c. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with categorical antiplatelet drug – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	**Full FI Adj HR (95% CI)**	**CHESS Adj HR (95% CI)**
	n=930	N=1066	N=1066
Model A Adjusted for age, sex only			
Not frail_no oral antiplatelet use	1.00	1.00	1.00
Not frail_use of non-ASA antiplatelet only	1.86 (0.52-6.75)	2.08 (0.81-5.35)	**2.30 (1.23-4.32)**
Not frail_use of 1+ ASA (with/without non-ASA) antiplatelet(s)	1.22 (0.79-1.89)	0.85 (0.61-1.19)	1.18 (0.89-1.57)
Frail_no oral antiplatelet use	**1.67 (1.23-2.27)**	**1.34 (1.04-1.71)**	**1.59 (1.20-2.11)**
Frail_use of non-ASA antiplatelet only	**3.12 (1.74-5.58)**	**2.56 (1.50-4.36)**	**2.87 (1.69-4.90)**
Frail_use of 1+ ASA (with/without non-ASA) antiplatelet(s)	**1.88 (1.37-2.58)**	**1.66 (1.20-2.30)**	**1.72 (1.32-2.23)**
Model B[†] Adjusted for age, sex, selected diagnoses			
Not frail_no oral antiplatelet use	1.00	1.00	1.00
Not frail_use of non-ASA antiplatelet only	1.89 (0.56-6.37)	2.11 (0.86-5.18)	**2.30 (1.19-4.42)**
Not frail_use of 1+ ASA (with/without non-ASA) antiplatelet(s)	1.19 (0.76-1.88)	0.83 (0.59-1.16)	1.15 (0.85-1.55)
Frail_no oral antiplatelet use	**1.63 (1.18-2.26)**	**1.30 (1.01-1.67)**	**1.54 (1.16-2.06)**
Frail_use of non-ASA antiplatelet only	**3.11 (1.75-5.51)**	**2.56 (1.54-4.23)**	**2.80 (1.73-4.54)**
Frail_use of 1+ ASA (with/without non-ASA) antiplatelet(s)	**1.73 (1.24-2.40)**	**1.57 (1.16-2.13)**	**1.60 (1.23-2.08)**

	CHSrel Adj HR (95% CI)	Full FI Adj HR (95% CI)	CHESS Adj HR (95% CI)
	n=930	N=1066	N=1066
Model C† Adjusted for age, sex, selected diagnoses, #hospitalizations/past year			
Not frail_no oral antiplatelet use	1.00	1.00	1.00
Not frail_use of non-ASA antiplatelet only	1.70 (0.55-5.26)	2.12 (0.93-4.79)‖	**2.02 (1.11-3.66)**
Not frail_use of 1+ ASA (with/without non-ASA) antiplatelet(s)	1.22 (0.77-1.95)	0.87 (0.62-1.20)	1.17 (0.88-1.57)
Frail_no oral antiplatelet use	**1.60 (1.14-2.25)**	**1.32 (1.03-1.70)**	**1.52 (1.13-2.05)**
Frail_use of non-ASA antiplatelet only	**2.97 (1.69-5.22)**	**2.41 (1.46-3.96)**	**2.78 (1.74-4.45)**
Frail_use of 1+ ASA (with/without non-ASA) antiplatelet(s)	**1.69 (1.21-2.38)**	**1.60 (1.20-2.13)**	**1.59 (1.22-2.08)**
Model D† Adjusted for age, sex, selected diagnoses, #hospitalizations/past year, # drugs‡			
Not frail_no oral antiplatelet use	1.00	1.00	1.00
Not frail_use of non-ASA antiplatelet only	1.52 (0.50-4.62)	2.06 (0.96-4.42)‖	**1.93 (1.06-3.54)**
Not frail_use of 1+ ASA (with/without non-ASA) antiplatelet(s)	1.27 (0.80-2.01)	0.88 (0.63-1.23)	1.16 (0.86-1.56)
Frail_no oral antiplatelet use	**1.60 (1.12-2.28)**	**1.31 (1.01-1.69)**	**1.48 (1.11-1.97)**
Frail_use of non-ASA antiplatelet only	**2.73 (1.57-4.74)**	**2.23 (1.39-3.58)**	**2.53 (1.63-3.90)**
Frail_use of 1+ ASA (with/without non-ASA) antiplatelet(s)	**1.66 (1.17-2.34)**	**1.52 (1.14-2.01)**	**1.51 (1.16-1.96)**

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate $p<0.05$; ‖ $p<0.10$.
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models B-D: selected diagnoses adjusted for included stroke, hypertension, coronary heart disease, diabetes, lipid abnormality.
‡Drug number excludes use of antiplatelet(s)

Table 5.6.1d. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with oral antidiabetic – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	Full FI Adj HR (95% CI)	CHESS Adj HR (95% CI)
	n=930	N=1066	N=1066
Model A Adjusted for age, sex only			
Not frail - no oral antidiabetic use	1.00	1.00	1.00
Not frail – use of 1+ oral antidiabetic(s)	1.46 (0.89-2.39)	1.23 (0.81-1.86)	**1.45 (1.09-1.95)**
Frail – no oral antidiabetic use	**1.62 (1.22-2.17)**	**1.55 (1.19-2.01)**	**1.55 (1.30-1.85)**
Frail – use of 1+ oral antidiabetic(s)	**2.27 (1.56-3.30)**	**2.30 (1.66-3.18)**	**1.99 (1.42-2.80)**
Model B[†] Adjusted for age, sex, selected diagnoses			
Not frail – no oral antidiabetic use	1.00	1.00	1.00
Not frail – use of 1+ oral antidiabetic(s)	1.01 (0.56-1.85)	0.99 (0.57-1.74)	1.12 (0.76-1.65)
Frail – no oral antidiabetic use	**1.54 (1.15-2.05)**	**1.45 (1.12-1.87)**	**1.45 (1.20-1.75)**
Frail – use of 1+ oral antidiabetic(s)	1.48 (0.89-2.45)	**1.69 (1.05-2.71)**	1.45 (0.86-2.43)
Model C[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year			
Not frail – no oral antidiabetic use	1.00	1.00	1.00
Not frail – use of 1+ oral antidiabetic(s)	1.13 (0.59-2.15)	1.09 (0.61-1.95)	1.27 (0.84-1.91)
Frail – no oral antidiabetic use	**1.50 (1.10-2.03)**	**1.46 (1.12-1.89)**	**1.46 (1.21-1.76)**
Frail – use of 1+ oral antidiabetic(s)	1.58 (0.95-2.61)	**1.82 (1.12-2.97)**	1.52 (0.91-2.55)
Model D[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year, # drugs[‡]			
Not frail – no oral antidiabetic use	1.00	1.00	1.00
Not frail – use of 1+ oral antidiabetic(s)	1.23 (0.64-2.37)	1.15 (0.65-2.05)	1.30 (0.86-1.97)
Frail – no oral antidiabetic use	**1.49 (1.10-2.02)**	**1.44 (1.11-1.85)**	**1.45 (1.21-1.73)**
Frail – use of 1+ oral antidiabetic(s)	1.52 (0.91-2.55)	**1.70 (1.04-2.77)**	1.45 (0.86-2.44)

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate p<0.05.
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models B-D: selected diagnoses adjusted for included diabetes, congestive heart failure, lipid abnormality, hypertension, coronary heart disease.
‡drug number excludes use of oral antidiabetic(s)

Table 5.6.1e. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with insulin – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	**Full FI Adj HR (95% CI)**	**CHESS Adj HR (95% CI)**
	n=930	N=1066	N=1066
Model A Adjusted for age, sex only			
Not frail - no insulin use	1.00	1.00	1.00
Not frail – use of 1+ insulin(s)	1.18 (0.37-3.83)	1.25 (0.52-3.01)	1.55 (0.80-3.00)
Frail – no insulin use	**1.59 (1.20-2.10)**	**1.56 (1.23-1.98)**	**1.54 (1.29-1.84)**
Frail – use of 1+ insulin(s)	**2.42 (1.41-4.16)**	**2.01 (1.23-3.26)**	**1.89 (1.01-3.53)**
Model B[†] Adjusted for age, sex, selected diagnoses			
Not frail – no insulin use	1.00	1.00	1.00
Not frail – use of 1+ insulin(s)	0.82 (0.24-2.78)	0.92 (0.36-2.33)	1.15 (0.57-2.35)
Frail – no insulin use	**1.55 (1.17-2.05)**	**1.51 (1.21-1.90)**	**1.45 (1.20-1.76)**
Frail – use of 1+ insulin(s)	1.70 (0.98-2.97)	1.48 (0.91-2.41)	1.38 (0.74-2.55)
Model C[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year			
Not frail – no insulin use	1.00	1.00	1.00
Not frail – use of 1+ insulin(s)	0.74 (0.21-2.65)	0.92 (0.33-2.60)	1.24 (0.61-2.51)
Frail – no insulin use	**1.49 (1.10-2.01)**	**1.52 (1.21-1.91)**	**1.45 (1.19-1.77)**
Frail – use of 1+ insulin(s)	1.67 (0.95-2.94)	1.41 (0.88-2.26)	1.21 (0.62-2.34)
Model D[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year, # drugs[‡]			
Not frail – no insulin use	1.00	1.00	1.00
Not frail – use of 1+ insulin(s)	0.73 (0.21-2.58)	0.96 (0.35-2.61)	1.26 (0.62-2.54)
Frail – no insulin use	**1.43 (1.06-1.93)**	**1.46 (1.18-1.82)**	**1.42 (1.17-1.72)**
Frail – use of 1+ insulin(s)	1.74 (0.98-3.09)	1.42 (0.88-2.30)	1.24 (0.64-2.40)

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; CHESS=Changes in Health, End-Stage Disease; Signs, and Symptoms Scale; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate $p<0.05$.
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models B-D: selected diagnoses adjusted for included diabetes, congestive heart failure, hypertension, chronic obstructive pulmonary disease.
‡drug number excludes use of insulin

Table 5.6.1f. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with insulin/sulfonylurea – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	**Full FI Adj HR (95% CI)**	**CHESS Adj HR (95% CI)**
	n=930	N=1066	N=1066
Model A Adjusted for age, sex only			
Not frail - no insulin or sulfonylurea use	1.00	1.00	1.00
Not frail – use of insulin and/or sulfonylurea	1.42 (0.73-2.77)	1.13 (0.68-1.88)	**1.60 (1.00-2.55)**
Frail – no insulin or sulfonylurea use	**1.62 (1.22-2.15)**	**1.53 (1.21-1.93)**	**1.57 (1.31-1.88)**
Frail – use of insulin and/or sulfonylurea	**2.29 (1.52-3.45)**	**2.19 (1.53-3.13)**	**1.87 (1.30-2.69)**
Model B[†] Adjusted for age, sex, selected diagnoses			
Not frail – no insulin or sulfonylurea use	1.00	1.00	1.00
Not frail – use of insulin and/or sulfonylurea	1.04 (0.49-2.21)	0.92 (0.48-1.77)	1.25 (0.72-2.17)
Frail – no insulin or sulfonylurea use	**1.53 (1.14-2.03)**	**1.43 (1.14-1.79)**	**1.44 (1.18-1.76)**
Frail – use of insulin and/or sulfonylurea	1.61 (0.98-2.63)	**1.63 (1.10-2.42)**	1.39 (0.93-2.10)
Model C[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year			
Not frail – no insulin or sulfonylurea use	1.00	1.00	1.00
Not frail – use of insulin and/or sulfonylurea	1.06 (0.47-2.38)	0.94 (0.48-1.85)	1.33 (0.78-2.28)
Frail – no insulin or sulfonylurea use	**1.49 (1.10-2.01)**	**1.44 (1.14-1.82)**	**1.46 (1.19-1.78)**
Frail – use of insulin and/or sulfonylurea	1.60 (0.98-2.62)	**1.62 (1.11-2.36)**	1.33 (0.89-2.00)
Model D[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year, # drugs[‡]			
Not frail – no insulin or sulfonylurea use	1.00	1.00	1.00
Not frail – use of insulin and/or sulfonylurea	1.08 (0.47-2.49)	1.00 (0.51-1.97)	1.34 (0.78-2.32)
Frail – no insulin or sulfonylurea use	**1.45 (1.08-1.95)**	**1.42 (1.14-1.76)**	**1.44 (1.19-1.76)**
Frail – use of insulin and/or sulfonylurea	1.63 (0.97-2.74)	**1.60 (1.08-2.38)**	1.37 (0.90-2.09)

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.

§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate $p<0.05$.
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models B-D: selected diagnoses adjusted for included diabetes, congestive heart failure, lipid abnormality, hypertension, coronary heart disease, chronic obstructive pulmonary disease.
‡drug number excludes use of insulin and sulfonylurea agent

When considering different types of antiplatelet use (see table 5.6.1c), the highest risk was associated with frail individuals using non-ASA antiplatelet agents, regardless of frailty measure used. Frail individuals using one or more ASA antiplatelet agents (with or without non-ASA antiplatelet) were also at a significantly increased risk when compared to non-frail non-antiplatelet users. However, the magnitude of the risk was considerably lower among frail residents using ASA antiplatelet agents compared to those using non-ASA (e.g., HR = 2.73 for CHS frail users of non-ASA antiplatelets, HR = 1.66 for CHS frail users of ASA antiplatelets in fully adjusted models). The risk of first-event hospitalization was also elevated in non-frail individuals using non-ASA antiplatelet agents when compared to non-frail non-antiplatelet users; this risk was significant when CHESS was used to classify frailty and marginally significant when the Full FI was used.

Table 5.6.1g. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with diabetic drug – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	**Full FI Adj HR (95% CI)**	**CHESS Adj HR (95% CI)**
	n=930	N=1066	N=1066
Model A Adjusted for age, sex only			
Not frail - no insulin or oral antidiabetic use	1.00	1.00	1.00
Not frail – use of insulin and/or oral antidiabetic(s)	1.42 (0.85-2.36)	1.27 (0.87-1.85)	**1.58 (1.17-2.12)**
Frail – no insulin or oral antidiabetic use	**1.59 (1.18-2.15)**	**1.52 (1.18-1.96)**	**1.57 (1.31-1.87)**
Frail – use of insulin and/or oral antidiabetic(s)	**2.44 (1.69-3.52)**	**2.35 (1.70-3.25)**	**2.09 (1.52-2.87)**
Model B[†] Adjusted for age, sex, selected diagnoses			
Not frail – no insulin or oral antidiabetic use	1.00	1.00	1.00
Not frail – use of insulin and/or oral antidiabetic(s)	1.15 (0.58-2.27)	1.22 (0.70-2.11)	1.40 (0.93-2.13)
Frail – no insulin or oral antidiabetic use	**1.51 (1.12-2.05)**	**1.43 (1.12-1.84)**	**1.44 (1.19-1.76)**
Frail – use of insulin and/or oral antidiabetic(s)	**1.82 (1.04-3.18)**	**2.00 (1.22-3.30)**	**1.72 (1.02-2.90)**
Model C[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year			
Not frail – no insulin or oral antidiabetic use	1.00	1.00	1.00
Not frail – use of insulin and/or oral antidiabetic(s)	1.30 (0.62-2.72)	1.35 (0.79-2.30)	**1.57 (1.06-2.33)**
Frail – no insulin or oral antidiabetic use	**1.48 (1.08-2.04)**	**1.46 (1.13-1.88)**	**1.46 (1.20-1.77)**
Frail – use of insulin and/or oral antidiabetic(s)	**1.98 (1.15-3.41)**	**2.12 (1.32-3.39)**	**1.78 (1.09-2.91)**
Model D[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year, # drugs[‡]			
Not frail – no insulin or oral antidiabetic use	1.00	1.00	1.00
Not frail – use of insulin and/or oral antidiabetic(s)	1.30 (0.61-2.80)	1.36 (0.79-2.33)	**1.53 (1.02-2.31)**
Frail – no insulin or oral antidiabetic use	**1.46 (1.06-2.00)**	**1.43 (1.12-1.83)**	**1.45 (1.20-1.75)**
Frail – use of insulin and/or oral antidiabetic(s)	**1.90 (1.08-3.32)**	**1.96 (1.22-3.17)**	**1.68 (1.02-2.78)**

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.

§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate $p<0.05$.
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models B-D: selected diagnoses adjusted for included diabetes, congestive heart failure, lipid abnormality, hypertension, coronary heart disease, chronic obstructive pulmonary disease.
‡Drug number excludes use of insulin and oral antidiabetic agents

Table 5.6.1h displays the results of the survival analysis models for exposure to the high-risk drug classes in combination. For all models using CHSrel and Full FI to identify frailty (and models A and B using CHESS), a dose-response effect was observed in which the risk of hospitalization increased among frail individuals with use of medications from more high-risk drug classes. In the fully adjusted models (model D), for all frailty measures, the risk of first event hospitalization in frail residents using medications from one HR drug class and in frail residents using medications from two or more HR drug classes, were significantly elevated over the risk in the reference group (non-frail individuals not using any HR drugs). For models in which CHSrel or the Full FI were used to identify frailty, frail residents using drugs from two or more HR classes were at highest risk of first-event hospitalization. When CHESS was used to identify frailty, the highest risk was associated with frailty and use of medications from one HR class.

Table 5.6.1h. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with # high-risk drug – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	**Full FI Adj HR (95% CI)**	**CHESS Adj HR (95% CI)**
	n=930	N=1066	N=1066
Model A Adjusted for age, sex only			
Not frail_no use of any of the 4 HR classes	1.00	1.00	1.00
Not frail_use of 1 HR drug class	1.63 (0.96-2.79)[‖]	0.98 (0.65-1.47)	1.27 (0.90-1.79)
Not frail_use of 2+ HR drug classes	1.64 (0.84-3.20)	1.11 (0.66-1.87)	**2.00 (1.37-2.94)**
Frail_no use of any of the 4 HR classes	**1.88 (1.24-2.84)**	1.18 (0.82-1.70)	**1.62 (1.17-2.24)**
Frail_use of 1 HR drug class	**2.27 (1.46-3.54)**	**1.69 (1.15-2.49)**	**2.02 (1.46-2.80)**
Frail_use of 2+ HR drug classes	**3.29 (2.01-5.38)**	**2.37 (1.50-3.74)**	**2.40 (1.60-3.60)**
Model B[†] Adjusted for age, sex, selected diagnoses			
Not frail_no use of any of the 4 HR classes	1.00	1.00	1.00
Not frail_use of 1 HR drug class	1.66 (0.97-2.83)[‖]	1.02 (0.67-1.57)	1.27 (0.89-1.82)
Not frail_use of 2+ HR drug classes	1.34 (0.66-2.73)	1.02 (0.56-1.84)	**1.71 (1.10-2.64)**
Frail_no use of any of the 4 HR classes	**1.84 (1.19-2.84)**	1.23 (0.83-1.82)	**1.55 (1.11-2.15)**
Frail_use of 1 HR drug class	**2.13 (1.34-3.39)**	**1.68 (1.12-2.52)**	**1.84 (1.30-2.60)**
Frail_use of 2+ HR drug classes	**2.56 (1.53-4.29)**	**2.06 (1.19-3.57)**	**1.89 (1.19-3.01)**
Model C[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year			
Not frail_no use of any of the 4 HR classes	1.00	1.00	1.00
Not frail_use of 1 HR drug class	1.67 (0.98-2.86)[‖]	1.06 (0.69-1.63)	1.25 (0.87-1.79)
Not frail_use of 2+ HR drug classes	1.29 (0.63-2.64)	1.08 (0.59-1.95)	**1.82 (1.18-2.78)**
Frail_no use of any of the 4 HR classes	**1.80 (1.16-2.81)**	1.27 (0.85-1.90)	**1.55 (1.10-2.18)**
Frail_use of 1 HR drug class	**2.12 (1.32-3.40)**	**1.73 (1.15-2.61)**	**1.90 (1.34-2.69)**
Frail_use of 2+ HR drug classes	**2.47 (1.47-4.14)**	**1.99 (1.13-3.51)**	**1.71 (1.06-2.76)**
Model D[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year, # drugs[‡]			
Not frail_no use of any of the 4 HR classes	1.00	1.00	1.00
Not frail_use of 1 HR drug class	1.66 (0.96-2.85)[‖]	1.04 (0.68-1.59)	1.23 (0.86-1.75)
Not frail_use of 2+ HR drug classes	1.27 (0.63-2.57)	1.04 (0.57-1.88)	**1.72 (1.12-2.64)**
Frail_no use of any of the 4 HR classes	**1.82 (1.17-2.84)**	1.26 (0.85-1.86)	**1.53 (1.09-2.15)**
Frail_use of 1 HR drug class	**2.03 (1.26-3.27)**	**1.63 (1.09-2.45)**	**1.79 (1.27-2.52)**
Frail_use of 2+ HR drug classes	**2.32 (1.39-3.87)**	**1.84 (1.06-3.20)**	**1.60 (1.00-2.54)**

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate $p<0.05$; || $p<0.10$.
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models B-D: selected diagnoses adjusted for included stroke, coronary heart disease, congestive heart failure, cardiac dysrhythmias, venous disorders, hypertension, diabetes, lipid abnormality, chronic obstructive pulmonary disease, dementia, schizophrenia, anxiety, depression.
‡Drug number excludes use of drug(s) of interest

Table 5.6.1i. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with antipsychotic – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	Full FI Adj HR (95% CI)	CHESS Adj HR (95% CI)
	n=930	N=1066	N=1066
Model A Adjusted for age, sex only			
Not frail - no antipsychotic use	1.00	1.00	1.00
Not frail – use of 1+ antipsychotic(s)	0.66 (0.41-1.06)	**0.63 (0.40-0.98)**	1.02 (0.71-1.48)
Frail – no antipsychotic use	**1.47 (1.06-2.04)**	**1.45 (1.09-1.92)**	**1.54 (1.26-1.89)**
Frail – use of 1+ antipsychotic(s)	**1.51 (1.05-2.15)**	**1.50 (1.11-2.02)**	**1.48 (1.06-2.07)**
Model B[†] Adjusted for age, sex, selected diagnoses			
Not frail – no antipsychotic use	1.00	1.00	1.00
Not frail – use of 1+ antipsychotic(s)	0.70 (0.42-1.15)	0.71 (0.44-1.14)	1.08 (0.73-1.59)
Frail – no antipsychotic use	**1.44 (1.04-2.01)**	**1.53 (1.16-2.04)**	**1.53 (1.25-1.87)**
Frail – use of 1+ antipsychotic(s)	**1.59 (1.08-2.34)**	**1.73 (1.23-2.44)**	**1.59 (1.13-2.25)**
Model C[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year			
Not frail – no antipsychotic use	1.00	1.00	1.00
Not frail – use of 1+ antipsychotic(s)	0.72 (0.43-1.21)	0.70 (0.43-1.14)	1.07 (0.73-1.59)
Frail – no antipsychotic use	1.41 (0.98-2.01)	**1.47 (1.09-1.98)**	**1.47 (1.20-1.80)**
Frail – use of 1+ antipsychotic(s)	**1.60 (1.08-2.37)**	**1.74 (1.24-2.43)**	**1.63 (1.16-2.29)**
Model D[†] Adjusted for age, sex, selected diagnoses, #hospitalizations/past year, # drugs[‡]			
Not frail – no antipsychotic use	1.00	1.00	1.00
Not frail – use of 1+ antipsychotic(s)	0.72 (0.43-1.21)	0.71 (0.44-1.15)	1.09 (0.74-1.59)
Frail – no antipsychotic use	1.39 (0.96-2.00)	**1.38 (1.03-1.84)**	**1.41 (1.16-1.72)**
Frail – use of 1+ antipsychotic(s)	**1.59 (1.08-2.35)**	**1.63 (1.18-2.26)**	**1.56 (1.12-2.18)**

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index; CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate p<0.05.
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models B-D: selected diagnoses adjusted for included dementia, schizophrenia, anxiety, depression.
‡drug number excludes use of antipsychotic(s)

5.6.2 Cox Proportional Hazards Models: High-Risk and Antipsychotic Medication Use, Frailty and Hospitalization (Comparator Groups: Non-frail Medication Users)

In order to more directly compare the impact of frailty as a modifier of the association between high-risk (HR) or antipsychotic medication use and hospitalization, analyses were conducted using different comparator (reference) groups. For the following results, the reference group for each of the medication classes of interest was non-frail residents who were using at least one medication from the class. Changing the reference group allows for examination of whether there is a significant difference in the observed risk of hospitalization among the different levels of frailty-medication use for each of the medication classes (i.e., among the levels presented in each of tables 5.6.1a-5.6.1i).

Table 5.6.2a displays hazard ratios for first-event hospitalization when non-frail residents who were using the medication of interest were used as the reference group. Findings for oral antidiabetic use or insulin use (and any combination of the two classes) were not found to be significantly associated with increased risk of hospitalization in frail residents, compared to non-frail residents, and are not shown.

Table 5.6.2a. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with selected drug – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	Full FI Adj HR (95% CI)	CHESS Adj HR (95% CI)
	n=930	N=1066	N=1066
Anticoagulant Use			
Model A[†]			
Reference: not frail - use of 1+ anticoagulant(s)			
Not frail – no anticoagulant use	0.87 (0.46-1.63)	0.98 (0.58-1.64)	**0.70 (0.49-0.99)**
Frail – no anticoagulant use	1.36 (0.77-2.42)	1.46 (0.96-2.21)[‖]	1.09 (0.79-1.51)
Frail – use of 1+ anticoagulant(s)	1.77 (0.95-3.29)[‖]	**2.03 (1.36-3.03)**	1.31 (0.93-1.86)
Model D[†]			
Reference: not frail - use of 1+ anticoagulant(s)			
Not frail – no anticoagulant use	0.98 (0.48-2.01)	1.01 (0.59-1.71)	0.73 (0.51-1.05)[‖]
Frail – no anticoagulant use	1.40 (0.73-2.68)	1.38 (0.90-2.10)	1.05 (0.76-1.45)
Frail – use of 1+ anticoagulant(s)	1.61 (0.83-3.13)	**1.64 (1.06-2.53)**	1.05 (0.71-1.55)
Antiplatelet Use			
Model A[†]			
Reference: not frail - use of 1+ antiplatelet(s)			
Not frail – no antiplatelet use	0.80 (0.52-1.23)	1.08 (0.77-1.53)	0.79 (0.59-1.05)
Frail – no antiplatelet use	1.33 (0.89-2.00)	**1.45 (1.06-1.98)**	**1.26 (1.00-1.58)**
Frail – use of 1+ antiplatelet(s)	**1.60 (1.03-2.48)**	**1.90 (1.29-2.79)**	**1.44 (1.12-1.86)**
Model D[†]			
Reference: not frail - use of 1+ antiplatelet(s)			
Not frail – no antiplatelet use	0.78 (0.50-1.24)	1.05 (0.75-1.46)	0.82 (0.61-1.10)
Frail – no antiplatelet use	1.25 (0.82-1.91)	1.37 (0.99-1.88)[‖]	1.21 (0.96-1.53)
Frail – use of 1+ antiplatelet(s)	1.38 (0.88-2.14)	**1.66 (1.15-2.38)**	**1.31 (1.01-1.70)**
Antipsychotic Use			
Model A[†]			
Reference: not frail - use of 1+ antipsychotic(s)			
Not frail – no antipsychotic use	1.52 (0.95-2.45)[‖]	**1.59 (1.02-2.49)**	0.98 (0.68-1.41)
Frail – no antipsychotic use	**2.24 (1.34-3.74)**	**2.31 (1.41-3.78)**	**1.51 (1.05-2.17)**
Frail – use of 1+ antipsychotic(s)	**2.29 (1.39-3.78)**	**2.38 (1.47-3.86)**	1.45 (0.92-2.72)
Model D[†]			
Reference: not frail - use of 1+ antipsychotic(s)			
Not frail – no antipsychotic use	1.39 (0.82-2.33)	1.41 (0.87-2.28)	0.92 (0.63-1.35)
Frail – no antipsychotic use	**1.92 (1.10-3.35)**	**1.94 (1.19-3.17)**	1.30 (0.88-1.92)
Frail – use of 1+ antipsychotic(s)	**2.20 (1.30-3.74)**	**2.30 (1.43-3.70)**	1.44 (0.91-2.26)

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index, CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.

§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate $p<0.05$; || $p<0.10$
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models A: adjusted for age and sex only; Models D: adjusted for age, sex, selected diagnoses (see tables5.6.1a, 5.6.1b, 5.6.1i), # hospitalizations/past year, # drugs (excluding drug(s) of interest).

As shown in table 5.6.2a, only residents using anticoagulants who were considered frail by the Full FI were at a statistically significant increased risk of first-event hospitalization in the fully-adjusted models (HR = 1.64, 95% CI 1.06-2.53) when compared to robust residents using oral anticoagulants.

With robust residents using antiplatelet agents as the reference group, Full FI frail residents using antiplatelets had the greatest associated risk of hospitalization (HR = 1.66, 95% CI 1.15-2.38), while CHESS frail residents using antiplatelet agents also had a statistically significant increased risk (HR = 1.31, 95% CI 1.01-1.70). However, looking specifically at ASA antiplatelet use, there was no significant difference in risk for frail individuals using these drugs compared to non-frail individuals using these drugs, regardless of frailty measure used (see table 5.6.2b).

With a reference group of non-frail residents using one or more antipsychotic agents, individuals who were classified as frail, according to CHSrel and the Full FI were at a significantly elevated risk for first-event hospitalization (regardless of antipsychotic medication use status). For both frailty measures, frail individuals who were using antipsychotic agents were at the highest risk. Individuals identified as frail by the Full FI who were using antipsychotics were at the greatest risk for first-event hospitalization (HR = 2.30, 95% CI 1.43-3.70), followed by CHSrel frail individuals using antipsychotics (HR = 2.20, 95% CI 1.43-3.70). In model A, individuals who were identified as frail by CHESS and were not using antipsychotic agents had a significantly elevated risk, compared to non-frail antipsychotic users; however, this risk was no longer significant in the fully adjusted model. CHESS frail individuals using one or more antipsychotic

agents were not at a significantly increased risk of hospitalization, when compared to non-frail antipsychotic users, in any of the models.

Table 5.6.2b. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with ASA/non-ASA antiplatelet – frailty[¶] measures, DAL Residents (n=1,066).

	CHSrel Adj HR (95% CI)	**Full FI Adj HR (95% CI)**	**CHESS Adj HR (95% CI)**
	n=930	N=1066	N=1066
Reference: not frail – non-ASA antiplatelet only			
Model A[†]			
Not frail – no antiplatelet use	0.54 (0.15-1.94)	0.48 (0.19-1.24)	**0.44 (0.23-0.81)**
Not frail – use of ASA (with/without non-ASA)	0.66 (0.19-2.30)	0.41 (0.16-1.03)‖	**0.52 (0.29-0.91)**
Frail – no antiplatelet use	0.90 (0.25-3.21)	0.64 (0.26-1.58)	0.69 (0.42-1.16)
Frail – use of ASA (with/without non-ASA)	1.01 (0.28-3.67)	0.80 (0.33-1.97)	0.75 (0.42-1.32)
Frail – use of non-ASA only	1.67 (0.48-5.83)	1.23 (0.48-3.17)	1.25 (0.71-2.21)
Model D[†]			
Not frail – no antiplatelet use	0.66 (0.22-2.01)	0.49 (0.23-1.04)‖	**0.52 (0.28-0.95)**
Not frail – use of ASA (with/without non-ASA)	0.84 (0.28-2.48)	**0.43 (0.20-0.92)**	0.60 (0.35-1.04)‖
Frail – no antiplatelet use	1.05 (0.36-3.12)	0.64 (0.31-1.31)	0.77 (0.47-1.24)
Frail – use of ASA (with/without non-ASA)	1.09 (0.37-3.12)	0.74 (0.36-1.51)	0.78 (0.46-1.33)
Frail – use of non-ASA only	1.80 (0.61-5.30)	1.08 (0.49-2.39)	1.31 (0.73-2.33)

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index, CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate $p<0.05$; ‖ $p<0.10$
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models A: adjusted for age and sex only; Models D: adjusted for age, sex, selected diagnoses (stroke, hypertension, coronary heart disease, diabetes, lipid abnormality), # hospitalizations/past year, # drugs (excluding drug(s) of interest).

As seen in table 5.6.2c, the hospitalization risk associated with use of any one HR medication class was significantly higher among frail residents compared to non-frail residents in fully adjusted models, when frailty was defined by the Full FI (HR = 1.57, 95% CI 1.15-2.14). A heightened risk was also observed for the use of two or more HR medication classes when Full FI frail residents were compared to non-frail residents (HR = 1.77, 95% CI 1.09-2.89).

Table 5.6.2c. Adjusted hazard ratios[§] (95% CIs) for hospitalization during 1-year follow-up associated with High-Risk Medication – frailty[¶] measures, DAL Residents (n=1,066).

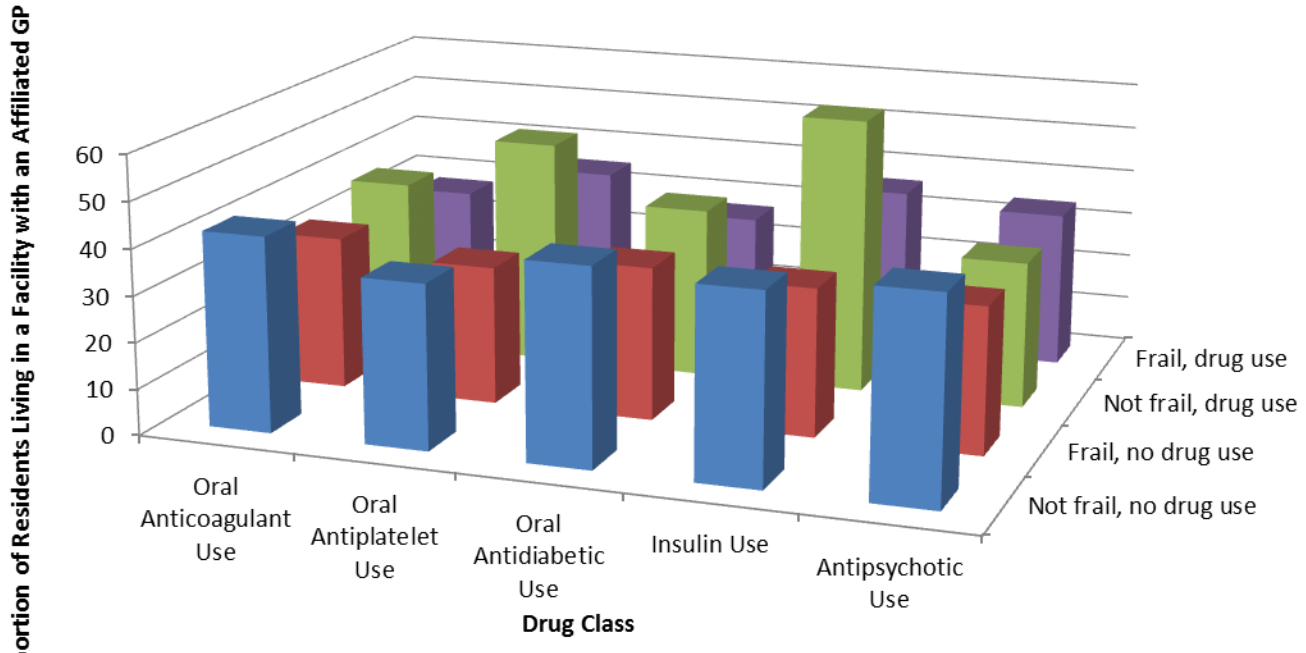
	CHSrel Adj HR (95% CI)	Full FI Adj HR (95% CI)	CHESS Adj HR (95% CI)
	n=930	N=1066	N=1066
Reference: not frail - use of drugs from 1 HR class			
Model A[†]			
Not frail – no HR drug use	0.61 (0.36-1.05)‖	1.02 (0.68-1.53)	0.79 (0.56-1.12)
Not frail – use of 2+ HR classes	1.00 (0.59-1.71)	1.13 (0.74-1.73)	**1.58 (1.16-2.16)**
Frail – no HR drug use	1.15 (0.77-1.73)	1.20 (0.88-1.65)	1.28 (0.95-1.73)
Frail – use of 1 HR class	1.39 (0.96-2.02)‖	**1.73 (1.28-2.33)**	**1.60 (1.26-2.02)**
Frail – use of 2+ HR classes	**2.02 (1.34-3.04)**	**2.41 (1.73-3.37)**	**1.89 (1.35-2.66)**
Model D[†]			
Not frail – no HR drug use	0.60 (0.35-1.04)‖	0.96 (0.63-1.46)	0.81 (0.57-1.16)
Not frail – use of 2+ HR classes	0.77 (0.41-1.44)	1.00 (0.63-1.58)	1.40 (0.95-2.05)‖
Frail – no HR drug use	1.10 (0.74-1.64)	1.20 (0.88-1.66)	1.25 (0.93-1.67)
Frail – use of 1 HR class	1.23 (0.85-1.79)	**1.57 (1.15-2.14)**	**1.45 (1.10-1.93)**
Frail – use of 2+ HR classes	1.40 (0.85-2.32)	**1.77 (1.17-2.67)**	1.30 (0.85-1.99)
Reference: not frail - use of drugs from 2+ HR classes			
Model A[†]			
Not frail – no HR drug use	0.61 (0.31-1.19)	0.90 (0.54-1.51)	**0.50 (0.34-0.73)**
Not frail – use of 1 HR class	1.00 (0.58-1.70)	0.88 (0.58-1.35)	**0.63 (0.46-0.86)**
Frail – no HR drug use	1.15 (0.64-2.07)	1.06 (0.70-1.62)	0.81 (0.57-1.16)
Frail – use of 1 HR class	1.39 (0.79-2.42)	1.52 (0.96-2.41)‖	1.01 (0.76-1.34)
Frail – use of 2+ HR classes	**2.01 (1.07-3.77)**	**2.13 (1.29-3.51)**	1.20 (0.83-1.73)
Model D[†]			
Not frail – no HR drug use	0.79 (0.39-1.58)	0.96 (0.53-1.74)	**0.58 (0.38-0.90)**
Not frail – use of 1 HR class	1.30 (0.70-2.44)	1.01 (0.63-1.59)	0.72 (0.50-1.05)‖
Frail – no HR drug use	1.43 (0.73-2.82)	1.21 (0.76-1.92)	0.89 (0.60-1.33)
Frail – use of 1 HR class	1.60 (0.85-3.00)	1.57 (0.945-2.62)‖	1.04 (0.73-1.50)
Frail – use of 2+ HR classes	1.82 (0.92-3.62)‖	**1.77 (1.09-2.89)**	0.93 (0.62-1.39)

Abbreviations: DAL=designated assisted living; CHSrel=Cardiovascular Health Study Frailty Criteria (with relative cut-points); Full FI=Full Frailty Index, CHESS=Changes in Health, End-Stage Disease, Signs, and Symptoms Scale; CI=confidence interval.
§ Derived from Cox proportional hazards regression models (first event analysis), also adjusted for clustering by facility; sample excludes 3 residents with unknown outcome who discontinued study and 20 who refused consent for administrative data linkage. Estimates in Bold indicate $p<0.05$; ‖ $p<0.10$
¶ For frailty measures, frail = frail + pre-frail residents (vs. not-frail)
† Models A: adjusted for age and sex only; Models D: adjusted for age, sex, selected diagnoses # hospitalizations/past year, # drugs (excluding drug(s) of interest);
Selected diagnoses adjusted for included stroke, coronary heart disease, congestive heart failure, cardiac dysrhythmias, venous disorders (see table 5.6.1a), hypertension, coronary heart disease, diabetes, lipid abnormality, chronic obstructive pulmonary disease

5.6.3 Facility Factors Associated with Frailty/Med Use

The categorical frailty – medication class variables were examined for their associations with certain facility-level factors relevant to medication oversight using chi-square analyses. For the purposes of these analyses, frailty as determined by the Full FI was used since this measure was most often observed to be an effect modifier of the drug exposure – hospitalization relationship. Few frailty–medication exposure variables were significantly associated with LPN/RN coverage (availability of licensed practical nurses [LPNs] and/or registered nurses [RNs] on site). However, it was observed that a significantly greater proportion of frail individuals using antipsychotics were residents of facilities with no LPN/RN coverage (25.5% of residents) when compared to non-frail residents using antipsychotic agents (13.6% of residents) (p-value = 0.0339, not shown in figure).

Figure 5.6.3a displays the proportion of residents living in a facility with an affiliated physician by their frailty - medication use status. Regardless of medication use status, the proportion of frail residents living in a facility with an affiliated GP was significantly lower than the proportion of non-frail residents. Furthermore, among frail residents using certain medication classes of interest (oral anticoagulants and oral antidiabetics), an even lower proportion of residents lived in facilities with an affiliated GP. When considering antipsychotic agents, frail antipsychotic users resided in facilities with physicians more often than non-frail antipsychotic users. However, residents who were non-frail and not using antipsychotic agents resided in facilities with physicians more frequently than residents who were frail and/or using antipsychotics.



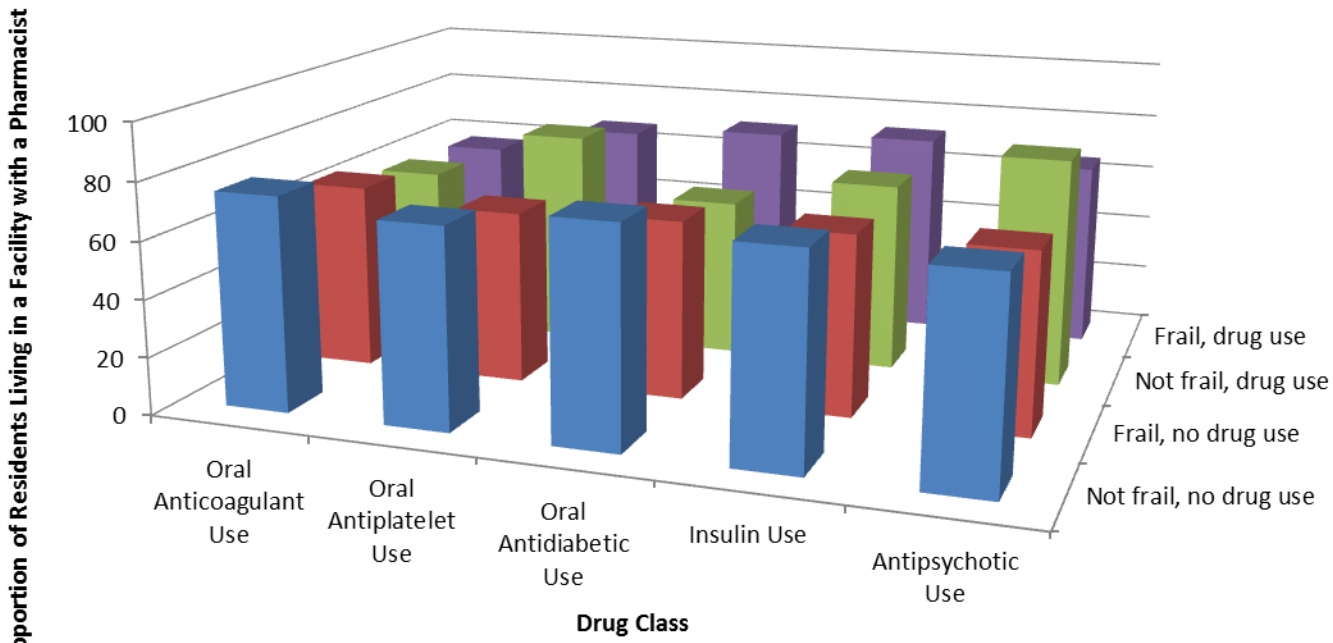
	Oral Anticoagulant Use*	Oral Antiplatelet Use*	Oral Antidiabetic Use*	Insulin Use*	Antipsychotic Use*
Not frail, no drug use	42.3	35.6	42.5	40.9	43.8
Frail, no drug use	33.3	30	33.2	32.1	31.7
Not frail, drug use	37.5	49.4	37.3	60	31.8
Frail, drug use	27.6	35	27.1	36.2	34

Figure 5.6.3a. Proportion of Residents Living in A Facility with an Affiliated GP‡ by Frailty†/Drug Use Status (n=1,066)

‡ GP / physician affiliated with the facility (with or without an office on site)

†Note: Frailty determined by Full FI, pre-frail subjects classified with frail subjects

*p-value < 0.05



	Oral Anticoagulant Use *	Oral Antiplatelet Use *	Oral Antidiabetic Use *	Insulin Use *	Antipsychotic Use *
Not frail, no drug use	74.8	69.8	75.8	72.9	70.9
Frail, no drug use	65.1	60.5	62.6	63.2	63
Not frail, drug use	58.3	76.3	55.9	66.7	80.3
Frail, drug use	56.9	67.4	70.8	72.3	65.6

Figure 5.6.3b. Proportion of Residents Living in A Facility with Pharmacist Involvement‡ by Frailty†/Drug Use Status (n=1,066)

‡ Pharmacist Involvement with the DAL residents as staff members or consultants in the facility during the last month

†Note: Frailty determined by Full FI, pre-frail subjects classified with frail subjects

*p-value < 0.05

The proportion of participants residing in facilities with pharmacist involvement by frailty - medication use status is shown in Figure 5.6.3b. In the case of oral anticoagulant use, oral antiplatelet use, and antipsychotic use, when comparing frail residents to non-frail residents based on medication-use status, the proportion of residents living in a facility with pharmacist involvement was significantly lower for frail residents than it was for non-frail residents. When considering oral antidiabetic use and insulin use, non-frail residents not using the drugs of interest most frequently lived in facilities with pharmacist involvement, compared to the other three frailty-medication use categories, followed by frail residents using the drugs of interest. Residents who were either frail or using medication from one of these two drug classes (oral antidiabetics and insulin) had a significantly lower probability of living in a facility with pharmacist involvement. Similar patterns were observed when the medication variable of interest was either use of any diabetic medication, or use of insulin and/or sulfonylurea.

6. DISCUSSION

Interpretation

The aim of the current research was to investigate whether selected measures of frailty act as effect modifiers of associations between certain high-risk and antipsychotic medications and hospitalization risk in a vulnerable older population. In order to address this question, the following research objectives were explored: the baseline distribution and resident-level correlates of (1a) frailty status (as identified by three measures of vulnerability), and (1b) high-risk/antipsychotic medication use, were investigated; (2a) associations between frailty status and first-event hospitalization were explored; (2b) associations between high-risk/antipsychotic medication use and first-event hospitalization were explored; and finally, (3) combined measures of frailty and high-risk/antipsychotic medication use were investigated for association with first-event hospitalization. The following sections address the interpretation of the research findings.

6.1 Univariate Descriptive Results

6.1.1 Baseline Resident Characteristics

The population studied in the ACCES designated assisted living (DAL) sample were more vulnerable than a community based sample of older adults, but less impaired than older adults residing in long-term care (LTC). Compared to the 2009 Canadian Community Health Survey (Healthy Aging),[162] the DAL residents participating in ACCES were observed to be older (48.9% over 85 v. 11.2%); have a higher proportion of female residents (76.7% v. 54.9%); greater activities of daily living (ADL) impairment (42.1% independent in ADLs v. 77.4%); and higher rates of diagnosed dementia (57.6% v. 1.6%), depression (34.3% v. 5.1%), and other co-morbid conditions, including hypertension (56.5% v. 50.2%), arthritis (53.8% v. 43.4%), heart disease

(29.2% v. 22.6%), osteoporosis (31.6% v. 18.1%), diabetes (22.6% v. 17.2%), COPD (18.4% v. 8.8%), and stroke (24.4% v. 4.2%).

As reported in previous ACCES publications,[112,163] compared to the ACCES LTC cohort, DAL residents had stronger social relationships, higher activity levels, fewer overall health concerns and comorbidities, lower levels of functional and cognitive impairment, and fewer mood and behavioural challenges, but had similarly high levels of medication use and were more likely to have been hospitalized in the year prior to baseline (see Appendix H).

The average age of the ACCES DAL residents, 84.9 ± 7.3, was similar to that observed in two US AL studies: 84.1 ± 7.7,[122] and 85.4 ± 8.6.[164] There was also a similar sex distribution, with 76.7% female in the ACCES population and 75.6% and 75.2% female in the two US assisted living (AL) populations.[122,164] However, the Alberta DAL population studied here had slightly higher rates of selected diagnoses including diabetes (22.6% v. 17.8%), CHF (22.4% v. 14.5%) and COPD (18.4% v. 10.5%), compared to one of the US AL studies.[164]

A high prevalence of diagnosed dementia was observed in the ACCES DAL cohort (57.6%), slightly higher than rates reported in a nationally representative US study, which reported a 42% prevalence of diagnosed dementia among AL residents.[165] The prevalence of depression observed in the ACCES DAL cohort (34.3%) was also similar but slightly higher than that reported in a Maryland AL sample (24%).[166] The high rates of dementia and mental health disorders among AL residents (along with associated medication use for management of behavioural and mood concerns)[165] add to the complexity of care and medication management for this vulnerable population.[165-167]

6.1.2 Baseline Facility Characteristics

Considering the vulnerability of the ACCES DAL sample in terms of age, comorbidity as well as cognitive and functional impairment, the limited skilled staffing available in many of these facilities, including LPN/RN staffing, physician affiliation and pharmacist involvement, is a source of concern. In particular, the absence of licensed practical nurse (LPN) and/or registered nurse (RN) staff in certain AL facilities poses concerns regarding the quality of care and oversight in these AL settings, which house over a quarter of residents identified in this study. An additional 10.8% of participating residents were living in a facility with LPN/RN staff on site for fewer than 24 hours/day, 7 days/week. Concerning figures have also been reported regarding the presence of licensed staff in AL facilities across the US, where it was noted that approximately one-quarter (24%) of facilities did not employ an RN or an LPN, while one-half (49%) had an RN and/or LPN on staff less than 24 hours/day.[168]

6.1.3 Baseline Medication Use

The proportion of residents using one or more antipsychotic agents in the ACCES DAL cohort was found to be 26.4%, similar to the 21% and 27.5% prevalence rates of antipsychotic use reported in US AL facilities,[167] and French AL facilities,[169] respectively. Higher rates of antipsychotic use were reported in ACCES LTC residents (32%)[158] and in Ontario LTC facilities (32.1% in 2010 and 28.8% in 2013),[170] as expected given the higher level of care in LTC compared to AL.

ACCES DAL residents had a similar, but slightly elevated prevalence of use of any diabetes medication (17.9%) compared to that reported in a Maryland AL study (14.6%).[113] Compared to residents of a Saskatchewan LTC facility, the ACCES DAL residents had a similar prevalence of oral antidiabetic medication use (14.4% in Alberta DAL, compared to 12.7% in Saskatchewan

LTC).[171] The proportion of residents using insulin was also similar across the three cohorts, with 5.8% of ACCES residents using insulin, and 5.6% of residents each from the Maryland AL study and the Saskatchewan LTC study. Additionally, 41.9% of insulin users in the Saskatchewan LTC study were observed to also be using oral antidiabetic agents, similar to the 39.7% of insulin users in the ACCES DAL cohort.

The prevalence of warfarin use among ACCES DAL residents was considerably higher, at 15.1%, than the 7.6% reported in the Maryland AL study.[113] Considerable variation in the prevalence of warfarin prescription in continuing care facilities was shown in a systematic review of warfarin use in LTC facilities, which reported prevalence rates from eight studies, ranging from 17% to 57% among those individuals with a condition for which warfarin was indicated.[172]

Prevalence of polypharmacy was similar among the ACCES DAL cohort (45.4% of residents using 9 or more distinct drugs), compared to the ACCES LTC cohort (42.7% of residents using 9 or more drugs), whereas Bronskill and colleagues[173] observed a much lower prevalence of polypharmacy among Ontario LTC residents (15.5% of residents using 9 or more distinct drugs). However, considerable variation was observed in polypharmacy prevalence between different Ontario LTC facilities (7.9% to 26.2%), and contrary to ACCES, non-prescription drugs were generally not included in medication counts in the Ontario LTC study.[173]

6.1.4 Baseline Frailty Measures

Examining the cohort of the Cardiovascular Health Study (the original cohort studied using the CHS frailty criteria), Fried and colleagues observed that the prevalence of frailty in the cohort was 6.9% and that 46.6% of the cohort were intermediate (pre-) frail.[80] Using similar cut-points

to those used in the CHS study, the prevalence of frailty in the ACCES cohort was 48.0%, with 48.5% pre-frail. Since the Cardiovascular Health Study was carried out in a community-dwelling population, it is not surprising that the prevalence of frailty in this population would be lower than that observed in the comparatively vulnerable ACCES DAL population. However, given that only 3.5% of the ACCES DAL cohort was identified as robust using this method, the use of the absolute cut-points for the CHS frailty measure would not be expected to differentiate well among the more vulnerable DAL residents examined here. Using the relative cut-points designed for this cohort (and used previously in ACCES studies),[123] a prevalence of 19.2% frail and 55.0% pre-frail was detected.

Another concern with respect to the CHS measures is the difficulty of obtaining all necessary information for the determination of frailty status from all residents, particularly for the performance-based items.[123] For some residents, missing CHS items were supplemented with similar items from the inter-RAI assessment in order to calculate the measure. However, the absence of certain items prevented the calculation of CHS frailty for 15% of residents. These feasibility concerns call into question the utility of the CHS measure as a means of identifying frailty in more vulnerable populations, such as residents of assisted living and continuing care settings.

Although Rockwood and colleagues (the developers of the FI) have stated that the FI is not meant to be categorized, in previous publications[174,175] they have offered various cut-points for classifying frailty, with FI=0.25 being the cut-point between pre-frail and frail in community-dwelling populations. In a study of French nursing home residents, it was concluded that a cut-point of 0.25 to identify frailty by the FI was inadequate for the NH population, identifying 64.8% of residents as frail.[176] The cut-points for classification of frailty (>0.3) and pre-frailty

(>0.2) used in the present study are the same as those used by Rockwood and colleagues in a nursing home population.[174]

Using the Full FI, the prevalence of frailty (27.5%) and pre-frailty (38.9%) were quite similar to the prevalence values obtained from community-dwelling older adults in the Canadian Community Health Survey (24% frail, 32% pre-frail) when different cut-off values were used (frailty=FI score > 0.21 vs. >0.3 for ACCES).[177] This observation is consistent with the expectation that DAL residents would be more vulnerable than community-dwelling older adults.

As with the absolute cut-points for the CHS measure, the Armstrong FI identified the vast majority of residents as frail or pre-frail (88.2%), limiting the ability of this measure to differentiate across the relative levels of vulnerability in this population.

Although CHESS is not specifically a frailty measure, it identified a similar proportion of frail and pre-frail residents (24.4%; 29.5%) as the Full FI (27.5%; 38.9%). CHESS and the Full FI also had a higher level of agreement (kappa = 0.36) than many of the other combinations of frailty measures (table 5.1.4), with only the two different versions of the FI having a higher level of agreement.

Given the generally low level of agreement between the frailty measures as well as the limited overlap observed between three of these measures in Figure 5.1.4b, it appears that these measures are not classifying the same residents as frail. It is possible that there is limited agreement between measures because each of the frailty measures is detecting different forms of vulnerability. Such a concept would not be surprising given the differing means of assessing vulnerability and the different interpretations of frailty associated with each of these measures.

6.1.5 Outcome

The cumulative incidence of first-event hospital admission over 1 year observed in the ACCES DAL cohort (38.7%)[112] was similar to the incidence reported in 2 US AL studies. Hedrick and colleagues[125] observed that 40.2% of assisted living residents in their study were admitted to hospital at least once over a year. Zimmerman and colleagues[122] observed a hospitalization rate of 12.7% per standardized 100-day quarter (46%–51% per year). The rate of hospitalization of AL residents has been observed to be higher than the hospitalization rate among LTC residents in both the ACCES study[112] as well as a US LTC study.[178]

6.2 Objective 1a: Examine Frailty Status (as identified by 3 measures of vulnerability) by Resident-Level Characteristics

6.2.1 Frailty Status by Resident-Level Characteristics

In the following section, only the three key frailty measures selected for the final analyses (objective 3, section 6.6) are discussed. A subsequent section (section 6.4) will include discussion of the five original frailty measures considered and the reasons for selecting the three key measures. With a few exceptions, the three key frailty measures considered were observed to be significantly associated with many of the same resident-level characteristics. The following are notable exceptions: CHESS vulnerability was not associated with increasing age or strength of social relationships, while the Full FI and CHSrel were; and CHSrel was not associated with cognitive function or aggressive behaviour, while the other frailty measures were.

The differences in resident-level correlates of the three frailty measures likely reflect the differing methods of assessing and identifying frailty. Frailty status defined by the Full FI was associated with almost every resident characteristic considered (with the exception of sex), perhaps because many of the characteristics considered are closely related to items in the Full FI

(see Appendix C). The association between the Full FI and a variety of resident characteristics is also consistent with the frailty index conceptualization of frailty as the accumulation of deficits across numerous domains.

There was no association between CHSrel frailty and cognitive impairment, or aggressive behaviour (which is frequently associated with dementia in continuing care populations). The absence of an association between CHSrel frailty and cognition-related characteristics may be explained by the items assessed in the CHS measure, which focus on physical and (to a certain extent) psychological items (e.g., questions for the exhaustion item, which are derived from a depression scale) to define frailty, without inclusion of items assessing cognition (see Appendix E). A 2007 study by Rockwood and colleagues[174] also reported that cognition was more highly correlated with the FI than with CHS, when using a different measure of cognition (3MS).

In contrast, the CHESS measure includes items related to physical function, disease status and cognition, but does not include any psychological or social items (see Appendix F), which may explain the absence of an association between CHESS and strength of social relationships. CHESS vulnerability was also observed to not be associated with age, unlike the other frailty measures. This is consistent with previous studies using CHESS, which showed a weak correlation between age and CHESS score.[88] This lack of association with age may be related to the fact that CHESS items are focused on acute measures of health instability (e.g., vomiting, changes in decision making or activity level over the past 90 days), which may make this measure more relevant to recent changes in health status that accompany disease, than it is to the slower progression of frailty related to accumulation of deficits or a changing phenotype over longer periods of time.

6.2.2 Frailty, Depression and Dementia

In a recent editorial, [91] Hubbard offered evidence that dementia and depression frequently coexist, along with frailty in older adults. She suggests that each of these three conditions is also likely to put older adults at greater risk for the development of the other two conditions. Analyses were carried out in order to examine the extent to which depression and dementia coexist with frailty, as defined by different frailty measures of interest.

For the purpose of the analysis underlying the Venn diagrams presented in section 5.2.2, 'frail' residents were restricted to those who had been classified as frail, and pre-frail residents were grouped with non-frail. Unlike the analyses for objective 3 (where frail and pre-frail residents were collapsed together because we wished to capture a broader range of vulnerability in relation to drug use and hospitalization risk), for the examination of coexisting dementia, depression and frailty, we were primarily interested in considering the condition or state of 'being frail' as specifically defined by the measures used.

The highest proportion of residents were identified as having frailty, depression and dementia when frailty was classified by the Armstrong FI. However, since the Armstrong FI identified more individuals as 'frail' than any of the other frailty measures, the higher degree of overlap across the three conditions may not reflect that Armstrong FI frailty coexists most often with the other two conditions. Indeed, of all of the frailty measures, the Armstrong FI classified the second highest number of residents with neither depression nor dementia as frail.

Frail residents, as classified by the Full FI, more frequently also had at least one of the two other conditions when compared to residents classified as frail by the other measures. Additionally, the

Full FI classification system resulted in the fewest total residents classified as only frail, without having either of the other two conditions.

There was moderate overlap between CHESS frailty and the other two conditions, with an equivalent proportion of frail residents having either depression or dementia as was observed using the Armstrong FI.

Regardless of the frailty measure used, there was always a higher proportion of frail residents with depression than frail residents without depression. However, using either CHS measure, there was a higher proportion of frail residents without dementia than frail residents with dementia. This may be explained by the fact that the CHS measure does not include any items pertaining to cognition, as explained above. Using the two CHS measures, the lowest proportion of residents identified as frail also had either dementia or depression, when compared to the other frailty measures.

It is not surprising that frailty, as defined by the FI, more frequently co-exists with dementia and depression when compared to frailty, as defined by CHS. Although the CHS measure includes an exhaustion item, which may serve as a marker of depression, it is mostly focused on physical or phenotypic decline. There are no items assessing cognition in the CHS measure. The FI, in contrast, focusing on accumulation of deficits across numerous domains, includes items related to cognitive and psychosocial concerns. In fact, according to the FI conceptualization of frailty, depression and dementia would be items that, when combined with other deficits, could lead to a state of frailty.

It is clear that depending on the measure used to classify frailty, the extent to which the condition co-exists with dementia and depression will vary. In order to understand the complex interplay

between these three conditions, it will be important to carefully consider the specific frailty measure used, and thus the conceptualization of frailty that is being investigated.

6.3 Objective 1b: Examine High-Risk and Antipsychotic Medication Use by Resident-Level Characteristics and by Frailty Status, as identified by 3 measures of vulnerability

6.3.1 High-Risk and Antipsychotic Medication Use by Resident -Level Characteristics

Findings regarding the distribution in use of many HR/antipsychotic medications by resident-level characteristics are, in many cases, likely related to the distribution of conditions indicating the use of these medications. For example, the higher rates of oral antidiabetic use in men, compared to women, is likely related to the higher incidence of diabetes in men compared to women, while decreased use of insulin and oral antidiabetic agents in those aged 80 and over compared to those aged 65-79 is supported by the decreased prevalence of diabetes among the oldest old in Canada.[179]

Antipsychotic use was observed to be significantly more common in those with fewer social supports (i.e., those who were never married/separated/divorced, compared to married residents; and those with low-no social relationships, compared with moderate-high social relationships). Possible explanations for this observation include close family members advocating for residents with dementia and opposing the use of antipsychotics, or informal caregivers easing the burden for AL staff, leading to decreased need for sedation of these residents. With respect to strength of social relationships, it is also possible that a portion of residents with dementia (frequent users of antipsychotic agents), have reduced capacity to maintain strong social relationships.

As expected, those with higher cognitive impairment (CPS score) were significantly more likely to be using antipsychotic agents. This observation is most likely reflective of the prescription of

antipsychotics to those with dementia (generally considered an off-label use of these agents), in order to sedate residents and control behavioural symptoms. It follows that residents with higher aggressive behaviour scores (ABS) would also be more likely to be using antipsychotic agents, a finding which was observed in this population.

The frequency of antipsychotic use among residents with dementia in this study is troubling given the increased risk of death associated with use of these drugs in those with dementia;[66-70] however, the observed prevalence appears to be consistent with rates reported in the literature. In a study of Ontario LTC residents, Bronskill and colleagues[173] observed that roughly 20.5% of residents were on antipsychotic agents with a diagnosis of dementia, consistent with the 20.7% (225/1089) of residents in the present study. The prevalence of antipsychotic use among nursing home residents with dementia was found to vary considerably among 8 European countries (Germany, England, Finland, France, Italy, Netherlands, Czech Republic, and Israel) ranging from 18% (Israel) to 60% (Czech Republic) with an average of 32.8%,[180] similar to the 35.9% (225/627) of ACCES DAL residents with dementia using antipsychotic agents. Despite the similar rates observed in LTC facilities across Ontario and Europe, there have also been findings from a previous ACCES study that rates of antipsychotic use among residents with dementia were significantly higher among DAL residents compared to LTC residents.[163]

For all medication classes studied, the prevalence of use of one or more medications from the drug class increased in those residents with higher levels of comorbidity (with the exception of oral antiplatelet agents), and with increasing levels of medication number. These findings are consistent with expectations since the medications considered are often used for the treatment of disease, and thus, use of the medications would be associated with comorbidity count. Additionally, use of medications from a specific drug class would be expected to be associated

with overall number of unique medications used, particularly since the medications of interest were not removed from the medication number variable for the purpose of these preliminary analyses (but were excluded from the drug count in all multivariable models, presented in sections 5.5-5.6).

Use of oral anticoagulants was found to be significantly associated with increasing number of hospital admissions in the previous year, whereas, use of antipsychotic agents was lowest among those who had experienced two or more hospital admissions in the past year. None of the other medication classes of interest were found to be significantly associated with previous hospitalizations. The association between use of oral anticoagulants and previous hospitalizations may be explained by the fact that anticoagulants would frequently be prescribed following a stroke or cardiac event which required hospitalization. Prescription of antipsychotic agents, in contrast, may be reconsidered upon hospitalization if the attending physicians feel that the patient is at risk of adverse events due to the drugs (or if a drug-related adverse event was the reason for hospitalization). Narrow therapeutic window (NTW) drugs are beneficial and often necessary, if used properly, and thus, it is unlikely that use of these drugs would be discontinued. Antipsychotic agents, in contrast, are frequently used in those with dementia, against recommendations, which may explain why antipsychotic use would be discontinued upon hospitalization.

6.3.2 High-Risk and Antipsychotic Medication Use by Frailty Status

The association observed between antipsychotic medication use and both Full FI frailty and CHESS instability is likely related to the cognition items included in each of these indices. These items increase the likelihood that residents with dementia, and resulting high rates of antipsychotic use, will be identified as frail (or at high risk) by these indices. No such association

was observed with CHSrel, likely because the CHS measure contains no items related to cognitive function.

Notably, although no significant associations were observed between the use of HR medication classes and frailty status (defined by any of the 3 key frailty measures, see table 5.3.2a-c), there were significant associations between the diagnoses potentially indicating use of certain HR medication classes and frailty status (see Appendix G). This may suggest potential under-treatment of medical conditions in frail individuals, or it may indicate rational prescribing to limit polypharmacy or burdensome therapies (potentially at the request of patient or family members) in frail patients. However, since many of the diagnoses considered were simply associated with use of the medication class, and did not necessarily represent indications for the use of the medication, it is difficult to conclude whether under-prescribing was a true concern. Furthermore, observed associations are likely related to the methodology for measuring frailty. For example, it is not surprising that diagnoses associated with use of each of the medication classes of interest were significantly associated with Full FI frailty status since many of these diagnoses would have counted as deficits contributing to the calculation of the frailty index.

6.4 Objective 2a: Examine Association between Frailty Status and First Event Hospitalization during a 1-year follow-up

6.4.1 Resident-Level Covariates and Outcome

The chi-square analyses revealed that DAL residents with higher levels of comorbidity, functional disability and social vulnerability were more often hospitalized compared to residents who were less vulnerable with respect to these characteristics. However, residents with greater vulnerability in terms of cognitive impairment and depression, as well as those exhibiting more aggressive behaviour were less likely to be hospitalized. Previous publications have observed

similar findings regarding decreased risk of hospitalization with increasing cognitive impairment among nursing home residents.[181-183]

Although residents with cognitive impairment and depression may be expected to be more vulnerable to adverse events compared to those without, it is possible that these residents are unlikely to recognize health concerns and/or communicate these concerns to AL staff, thus reducing the number of hospitalizations in these groups when compared to cognitively intact and non-depressed residents. These findings may also indicate a preference toward less aggressive treatment for depressed and cognitively impaired individuals. Notably, increased levels of cognitive impairment, depressive symptoms and aggressive behaviour are all associated with increased risk of first-event transfer to LTC or death, suggesting that these characteristics are indicative of increased vulnerability to adverse outcomes, even if they are not associated with increased rate of first-event hospitalization.

6.4.2. Bivariate Analyses: Frailty and Outcome

In bivariate analyses, all measures of vulnerability (CHSabs, CHSrel, Full FI, Armstrong FI, CHESS and fatigue) were found to be significantly associated with first-event outcome. However, Cox proportional hazards models revealed that only CHSrel, Full FI, and CHESS vulnerability as well as the single fatigue item from the interRAI-AL tool were significant risk factors for time to first-event hospitalization. No significant difference in risk of first-event hospitalization was observed among those with increasing levels of frailty, as judged by CHSabs or Armstrong FI. Both CHSabs and the Armstrong FI detected a high prevalence of frailty and pre-frailty among DAL residents, classifying only 3.5% and 11.8% of residents as robust, respectively. It is possible that these measures were not highly predictive of hospitalization because they did not differentiate between the higher degrees of vulnerability common in

assisted living residents. The paper by Armstrong and colleagues (which was used as the basis for development of the Armstrong FI used in the present study), reported that the Armstrong FI and CHESS were both significantly associated with adverse outcomes (institutionalization or death) for home care clients, but higher hazard ratios were observed for CHESS.[90] In previous publications from the ACCES study it has been observed that Armstrong FI frailty was significantly associated with an increased risk of death and transfer to long-term care, but not hospitalization.[85] CHSabs, as well, was more highly associated with risk of death or transfer to long-term care than with risk of hospitalization.[85]

In this analysis, the CHS frailty measure (relative cut-points), was found to be the most predictive of hospitalization. The Full FI was associated with a lower risk of first-event hospitalization than both CHSrel and CHESS. In a previous publication comparing the CHS frailty criteria to a deficit accumulation approach to detecting frailty (similar to the FI), Kulminski and colleagues observed that the deficit accumulation approach predicted mortality better than the CHS phenotypic approach.[161] It is clear that across different populations, settings, and outcomes considered, there is no consistently superior frailty measure for predicting adverse outcomes. Indeed, the definition and conceptualization of frailty, as well as the merit for inclusion of social, psychological and cognitive items in frailty measures has been an ongoing source of debate.[19,20,23]

In a previous ACCES study it was shown that the interRAI-AL measure of fatigue was highly associated with hospitalization.[85] In order to explore whether this single item could predict hospitalization with similar strength as the full measures, fatigue was included as a vulnerability measure in this analysis. In the survival analysis models, moderate to severe fatigue was found to be a strong predictor of hospitalization (adjusted HR = 1.81, 95% CI 1.37-2.40), second only to

CHSrel frailty (adjusted HR = 2.11, 95% CI 1.53-2.92). This finding suggests that a simple measure of fatigue may be worthy of exploration and further comparison with other vulnerability measures as a predictor of adverse outcomes. However, the fatigue variable considered here is an acute measure, defined as inability to complete normal daily activities in the past 3 days due to diminished energy. As such, it is possible that this measure of fatigue may not be a strong indicator of vulnerability to adverse events relating to prevalent use of high-risk medications.

For the remaining analyses, the CHSrel, Full FI and CHESS measures were selected in order to explore frailty as an effect modifier of the association between high-risk/antipsychotic medication use and hospitalization. This decision was made based on evidence from previous publications using ACCES data regarding the appropriateness of these measures for this population[85,123] as well as from preliminary analyses explored in this research.[85] The analyses discussed here offer further support for the selection of these measures as predictors of hospitalization. Additionally, the three measures selected each emphasize very different methodologies for detecting vulnerability, allowing for comparison of different conceptualizations of frailty.

6.5 Objective 2b: Examine Association between Exposure to High-Risk/Antipsychotic Medication Measures and First Event Hospitalization during a 1-year follow-up

Use of certain high-risk medication classes was associated with adverse first-event outcomes in the chi-square analysis, and with hospitalization in age- and sex-adjusted models. However, in fully-adjusted models, for the majority of medications considered, no significant association was observed between medication use and hospitalization. The risk associated with use of these medications in the age- and sex-adjusted models appears to have been strongly influenced by

confounding. In particular, it appears that confounding by indication was relevant in these analyses. For almost all medication classes considered, the hazard ratios dropped closer to one and were no longer significant after adjusting for the presence of selected diagnoses (which represented likely indications for use of the selected drug/drug class) and which would be expected to be independent risk factors for hospitalization.

The only medication class which remained significantly associated with first-event hospitalization in the fully-adjusted models was use of non-acetylsalicylic acid (ASA) antiplatelet agents (without ASA antiplatelet agents). It is possible that use of non-ASA antiplatelet agents causes adverse drug events or declining health, leading to higher rates of hospitalization. Use of clopidogrel (the primary non-ASA antiplatelet agent prescribed in this population) has been found to be associated with an increased risk of gastro-intestinal (GI) bleeding; however, the risk of such an adverse event was found to be higher with use of ASA than with use of clopidogrel, and highest with combined use of both ASA and coplidogrel.[184,185] Therefore, the risk of GI bleeding would not explain the elevated risk of hospitalization in those using non-ASA antiplatelets compared to those using ASA (with or without non-ASA) antiplatelets. Clopidogrel use has also been reported to be more effective than ASA at reducing the risk of stroke, myocardial infarction, and vascular death,[186] suggesting that the observed association is not related to limited effectiveness of non-ASA antiplatelet agents. However, it has been observed that risk of adverse events among patients with acute coronary symptoms increased significantly in the 90-day interval after discontinuing clopidogrel treatment.[187] Given that medication exposure was assessed at baseline during data collection for ACCES, the elevated risk of hospitalization observed in residents using non-ASA antiplatelet agents could be

related to the discontinuation of this medication at some point during the 1-year follow-up period and the increased risk of adverse events in the days following discontinuation.

It is also possible that the observed association is the result of confounding by indication, despite adjustment for possible confounders. The following scenarios are potential examples of how confounding by indication could lead to an observed association between non-ASA antiplatelet use and hospitalization: (i) non-ASA antiplatelet agents are preferentially used in those with a higher severity of disease, and the disease severity results in a higher likelihood of hospital admission; or (ii) residents who were using non-ASA antiplatelet agents were using these drugs because of existing health conditions contraindicating the use of ASA antiplatelet agents (other than the diagnoses adjusted for), and these health conditions were the reason for the increased risk of hospitalization.

In fact, clopidogrel has been reported to be more effective than ASA at preventing stroke in high-risk subgroups of patients[186,189] If clopidogrel, and other non-ASA antiplatelet agents are frequently used in those with a higher baseline risk of stroke, this could explain the higher hospitalization rate among non-ASA antiplatelet users.

Additionally, the 2002 recommendations on the treatment of patients with unstable angina, released by the American College of Cardiology/American Heart Association (ACA/AHF) Task Force, recommended the use of clopidogrel in patients who experienced gastrointestinal intolerance with the use of ASA.[190] Later studies revealed that clopidogrel was also associated with an increased risk of recurrent ulcer bleeding, suggesting that it is not a suitable alternative to ASA treatment for prevention of GI bleeding.[191] The 2008 version of the ACA/AHF recommendations no longer suggested clopidogrel for patients with GI concerns.[184] However,

given that the ACCES study began in 2006, it is possible that the elevated risk of hospitalization associated with use of non-ASA antiplatelet agents is related to the preferential use of clopidogrel over aspirin in residents with a history of GI concerns, as suggested in the 2002 recommendations, potentially resulting in higher rates of GI bleeding in those using non-ASA antiplatelets.

The combined measure of use of high-risk medication classes remained borderline significant in models B and C, but was no longer significant in model D, the fully adjusted model. In all models, the hazard ratio for hospitalization increased with increasing number of high-risk medication classes used. Considering the HR drug classes individually, the major risk associated with anticoagulant and antiplatelet use is bleeding,[192,193] while insulin and oral antidiabetic agents are associated with a risk of hypoglycemia or hyperglycemia if their use is not managed properly.[59.60] Certain oral antidiabetic agents have also been reported to be associated with risk of myocardial infarction and congestive heart failure.[194] It might be expected that there would be a higher risk of adverse outcomes in those using medications from more than one high-risk class because of the potential for interaction between different high-risk medications, which may impact the dosage and timing within which these medications are effective and safe; and because of the potential errors due to the management of multiple complex medication regimens. Indeed, the combined use of anticoagulant and antiplatelet agents has been associated with a heightened risk of bleeding compared to use of either individually.[192] Additionally, a higher risk of edema has been identified with combined use of insulin and certain oral antidiabetic agents (thiazolidinediones) compared to individual use.[195] With the combined HR medication classes variable and many of the other medication variables considered, it would be useful to conduct

analyses with a larger sample in order to investigate whether moderately elevated risks, such as those observed for this variable, would be statistically significant.

Baseline use of antipsychotics was found to be associated with a first-event outcome of death or transfer to LTC compared to other outcomes of interest in chi-square analyses. However, use of antipsychotic agents was not associated with hospitalization risk in any of the models. Major risks associated with antipsychotic use include falls,[31,64] worsening of symptoms of Parkinsonism,[75] as well as stroke[32] and sudden cardiac death, [33] particularly among those with dementia. [66,67,68]

6.6 Objective 3: Determine whether Frailty Measures act to modify the Associations between specific High-Risk Medication Use and Hospitalization during a 1-year Follow-up.

6.6.1 Cox Proportional Hazards Models: High-Risk and Antipsychotic Medication Use, Frailty and Hospitalization

When compared to a reference group of non-frail residents not using the drug of interest, frail residents using the medication were observed to be at the highest risk for most of the medication variables and frailty measures explored. In many of these cases, the risk among frail medication users was statistically significant (anticoagulants, antiplatelets, any diabetes medication, and antipsychotics agents, with any measure of frailty; oral antidiabetics and insulin/sulfonylurea, with Full FI frailty).

Of note were the findings for antipsychotic agents where a significantly heightened risk of hospitalization was observed in frail antipsychotic users compared to non-frail non-drug users, and a decreased risk of hospitalization was found in non-frail antipsychotic users. Although the decreased risk among non-frail users was not statistically significant, it is interesting to consider

that use of antipsychotic agents may increase risk of hospitalization in frail individuals, but have a protective effect in non-frail individuals. Given the high degree of overlap reported between frailty and dementia,[91] it is possible that the risk associated with antipsychotic use in individuals with dementia could be partially explained by frailty status.

Another notable observation involved the use of non-ASA antiplatelet agents. A heightened risk of hospitalization was observed in non-ASA antiplatelet users, which was significant for frail non-ASA users (for all three measures of frailty), but only significant in non-frail residents when frailty status was determined by CHESS. The highest risk was observed for frail non-ASA users and this risk was considerably higher in magnitude than the risk associated with any of the other frailty/antiplatelet use combinations, regardless of frailty measure used. As stated, the heightened risk of hospitalization in users of non-ASA antiplatelet agents may be related to some risk of adverse events resulting from use of these drugs, or it may result from confounding by some factor related to use of non-ASA antiplatelets over ASA antiplatelets. Regardless, frailty status (as measured by Full FI and CHS, in particular) appears to have differentiated a group of non-ASA antiplatelet users who were at a higher risk of hospitalization.

Although the models included adjustment for diagnoses which represented common indications for the medication of interest, information was not available regarding disease severity. Thus, it is possible that the combination of high-risk medication use and frailty status captured residents with higher disease severity, who thus would be expected to have a greater risk of hospitalization as a result of the severity of their disease status, rather than the effects of the medication. However, it is also possible that, as hypothesized, physiological changes resulting from a state of frailty alter the range at which high-risk medications are safe and effective, or that

cognitive/social/psychological deficits impact the management of medications, resulting in an increased number of adverse drug events from the use of NTW drugs.

6.6.2 Cox Proportional Hazards Models: High-Risk and Antipsychotic Medication Use, Frailty and Hospitalization (Comparator Groups: Non-frail Medication Users)

In order to allow for direct comparison of the effect of frailty on the hospitalization risk associated with use of HR/antipsychotic medications, analyses were conducted using a reference group of non-frail residents using the drug of interest (table 5.6.2a).

In fully adjusted models, the Full FI was the frailty measure that was most often associated with a significantly increased risk of hospitalization in residents using certain medication classes, when compared to non-frail users of the medication classes. When considering HR drugs, use of anticoagulants and use of antiplatelet agents were each associated with a significantly increased risk of hospitalization in Full FI frail residents (HR = 1.64, 95% CI 1.06-2.53; HR = 1.66, 95% CI 1.15-2.38, respectively). In most cases, the hazard ratios were elevated for frail non-users; however, these findings were not statistically significant in the fully adjusted model.

The other high-risk medication variables considered (oral antidiabetics, insulin, and combined variables of the two classes) were not associated with a significantly increased risk of hospitalization when frail users were compared to non-frail users. Given that there were relatively few residents using insulin or oral antidiabetic agents, it is not surprising that findings were non-significant. However, the evidence that the risk of hypoglycemia may be elevated in individuals with dementia using oral antidiabetics,[111] along with the frequent co-occurrence of dementia and frailty,[91] suggest that it may be worthwhile to explore this question further in a sample with more participants or with a higher proportion of diabetic participants.

Using both the Full FI and CHS measures, use of antipsychotic agents in frail individuals was significantly associated with first-event hospitalization when compared to non-frail users (see table 5.6.2a). Again, it is interesting to note that no association was observed between antipsychotic use and hospitalization risk in models that were not stratified by frailty. However, upon stratification, a significant risk associated with antipsychotic use in frail residents was observed. This finding may indicate that certain frailty measures can, in fact, be used to differentiate between individuals who are at risk of poor outcomes from the use of antipsychotics and individuals who benefit from their use.

6.6.3 Facility Factors Associated with Frailty/Medication Use

The observation that frail users of antipsychotics were more frequently residents of facilities with no oversight by registered nurses (RNs) or licensed practical nurses (LPNs) compared to non-frail users of antipsychotics is a troubling finding. As hypothesized in the present research, a state of frailty may increase the risks associated with the use of certain medications. Indeed, it was observed that frail individuals were at a higher risk of hospitalization compared to non-frail individuals when using antipsychotic medications. This finding suggests that the presence of skilled nursing staff (who are trained to monitor medication use and identify signs of adverse effects) in the AL facility may be particularly important in facilities where frail residents frequently use such medications. Indeed, it has been reported that a higher proportion of RN or LPN nursing staff hours in AL facilities may reduce the risk of hospitalization among residents.[121,122] Although frail residents using antipsychotic agents were more likely to reside in a facility with an affiliated general practitioner (GP) compared to non-frail residents using antipsychotics, an even greater proportion of residents living in a facility with an affiliated GP were non-frail and not using antipsychotics.

In fact, for all other medication classes of interest, non-frail residents using the medication of interest were more likely to be in a facility with an affiliated GP compared to frail residents using the medication of interest. These findings, again, raise concerns that individuals who are most vulnerable are living in the facilities with lower skilled staffing while comparatively robust individuals are living in facilities with greater oversight by skilled medical professionals. Similarly, non-frail residents not using the drug of interest (high-risk or antipsychotic medications) more frequently resided in facilities with pharmacist involvement compared to frail residents for all drugs considered. Although these observations may be a reflection of trained medical professionals acting to prevent the development of frailty or taking steps to reduce use of unnecessary medications by residents of these facilities, it may also demonstrate incompatibility between skilled staffing in AL facilities and the level of vulnerability and complexity of the residents. Such a discrepancy between the complexity of resident medication regimens and skill level of staff was also found in a US AL study.[113]

Strengths and Limitations

The present research has several strengths stemming from the strengths of the ACCES study. These include the large sample size of 1,066 participants, the relatively high response rate of 72%, linkage to validated data for the hospitalization outcome, inclusion of participants from a variety of different DAL facilities, and the collection of comprehensive prospective data. Additionally, the examination of first-event outcomes ensures that observed hospitalization events are related to care received in the AL facility and not related to another care transition; and the use of survival analysis methods optimizing the sample size by extracting information from participants censored prior to the study end date. Finally, compared to other studies which

often utilize data on prescribed or dispensed medication (not necessarily indicative of actual medications used), the collection of data on actual medication use is a strength of this study.

There are also some limitations that must be considered. Approximately 28% of eligible residents from participating AL facilities were not enrolled. Although the age and sex distribution of these individuals were similar to those of the participants, the generalizability of the study results may be limited. Enrollment into ACCES was restricted to residents of designated assisted living. These publicly subsidized AL facilities fall under regulation of the Alberta provincial health service and are accessed through a single point of entry. Thus, there may be concerns with generalizing the findings of this study to private-pay facilities or AL in other provinces. Despite this, there are common elements among all AL facilities which differentiate them from other settings.

The exposure of interest was the use of high-risk or antipsychotic medications. One limitation of the research approach is that prevalent, rather than incident, medication use is considered, allowing for the possibility of healthy user bias. Information on incident medication use was not available in the ACCES database, and if it were, consideration of incident, rather than prevalent, medication use would have considerably reduced the number of participants with the exposure of interest. Regardless, it is possible that by considering prevalent medication use, the present research has an exposure group made up of participants who are especially tolerant to these high-risk medications, while those who would be sensitive to adverse effects resulting from these drugs had already ceased taking them or been lost to follow-up due to death or transfer to LTC.

In addition to the limitations regarding potential healthy user bias, there are further limitations related to the exposure. The dose of medication used was not considered in analyses.

Additionally, the measure of medication use utilized was based on the baseline assessment only. Any potential changes in medication use over the follow-up period were not explored. However, concerns regarding changing medication exposure over the follow-up period or the potential for healthy user bias may be less problematic in this study, considering that the primary medication exposure of interest is high-risk medications. High-risk medications, as defined above, are necessary treatment for many older adults. Thus, discontinuation of the drugs following adverse effects would be less likely for users of these medications than for other, less essential pharmacotherapy.

The outcome of consideration for the present research was limited to hospitalization. It is possible that other outcomes are more relevant to high-risk medication use such as falls, functional decline or death (particularly in the case of antipsychotic use for those with dementia). Future studies with longer follow-up may be better suited to investigating such outcomes. Hospitalization was identified using provincial data. Thus, any hospitalization events that occurred outside of Alberta may be missed.

The current study did not assess the reason for hospitalization, and as such, there is no way to confirm whether the observed hospitalizations were related to medication use. Although most-responsible-diagnosis information was available through the Alberta Inpatient Discharge Abstract Database (and is shown in Appendix I), it is possible that observed hospitalization events could have been related to medication use, either directly or indirectly, without the knowledge of the health care provider, and could go unnoticed and unreported. As a result, limiting analyses to only those hospitalizations designated as adverse drug events would potentially overlook some important outcomes related to medication use.

Data collection for ACCES took place between 2006 and 2009. Given the changes that have taken place in Alberta AL facilities since that time, these data may not represent the most up-to-date trends in AL. Despite this limitation, the findings of this study will likely be applicable to AL facilities in Alberta and beyond with respect to the continued use of high-risk medications among vulnerable residents.

Almost 40% of participants did not complete one or both of the physical measures of the CHS frailty assessment. As pointed out in earlier publications from the ACCES study, the inability of some DAL residents to carry out the CHS frailty assessment as originally designed suggests that this assessment may not be a feasible means of identifying vulnerability in an AL setting.[85,123] In order to supplement missing data for those residents who did not complete the full CHS frailty assessment, responses to applicable questions from the interRAI-AL assessment were substituted. Using this modification, the proportion of participants with missing data for the CHS frailty assessment was reduced to 15%, decreasing the sample size to 930 for this measure. Modifications to the CHS frailty assessment have been necessary in other studies, including an analysis of frailty in the Women's Health and Aging Studies, carried out by Fried and colleagues.[196]

Despite these limitations, the present research offers some important insights into the feasibility of frailty as an indicator of vulnerability to adverse outcomes related to HR/antipsychotic medication use.

Implications and Future Research

The present research offers evidence suggesting that a state of frailty may increase the risk of adverse outcomes associated with the use of antipsychotic and high-risk medications. In

particular, the risk of hospitalization appears to be significantly elevated in frail individuals using oral anticoagulants, oral antiplatelet agents, medications from any HR drug class (particularly when two or more HR classes are used concurrently), and antipsychotic agents.

The inter-RAI CHESS measure of vulnerability was not particularly useful for differentiating risk associated with use of these medications; however, the CHS frailty measure, with relative cut-points, and in particular, the Full FI were often able to differentiate residents with a higher degree of vulnerability.

The observation that frail antipsychotic users were at a considerably elevated risk compared to non-frail antipsychotic users has interesting implications. It has been observed that antipsychotic use is associated with an increased risk of stroke, cardiac failure and death in individuals with dementia,[66,67,68] and the frequent co-occurrence of frailty and dementia has been highlighted by Hubbard.[91] However, even after controlling for dementia status, the risk among frail individuals using antipsychotic agents remained significantly elevated. Perhaps those individuals at highest risk due to the use of antipsychotic agents are not just those with dementia, but also frail individuals. Frailty status could be considered as a means for determining whether antipsychotic agents can be safely prescribed to certain older adults. However, further support for this research question in future studies would be necessary before such policies could be implemented.

The findings regarding non-ASA antiplatelet use are not fully understood. Frail users of non-ASA antiplatelet agents were found to be at the highest risk of hospitalization compared to the other possible frailty-antiplatelet use combinations. However, it appears that, unlike many of the other medication classes examined, a substantial portion of the observed risk was associated with use of the medication itself (and a smaller portion of the risk was associated with frailty status).

Additionally, unlike other medication exposures, it appears that the CHSrel frailty measure, rather than the full FI, may be the most suitable for differentiating levels of risk associated with use of non-ASA antiplatelet agents. There was limited evidence in the literature suggesting that there is a true increased risk resulting from non-ASA antiplatelet use compared to ASA use. However, possible explanations for the risk associated with non-ASA antiplatelet use include risk related to the discontinuation of these medications,[187] or confounding due to preferential use of non-ASA antiplatelets over ASA antiplatelets in those with a history of GI bleeding,[191] or those with a higher severity of disease.[188,189]

Given the strong associations between adverse drug events and the use of high-risk and antipsychotic medications in older adults,[30,55] using a frailty measure as a means of determining which older adults are more vulnerable to adverse outcomes may be advantageous for identifying those in need of careful medication management and additional monitoring by trained staff. Considering the findings suggesting that the presence of skilled medical staff in AL facilities is often not associated with higher levels of frailty or use of more complex medications, it may be particularly relevant to consider the level of medication monitoring available to vulnerable residents in these settings.

Although levels of comorbidity and physical impairment are generally lower in AL facilities, compared to LTC facilities, a high prevalence of dementia and mental health concerns have been observed in the ACCES DAL cohort, as well as other AL studies.[165,166] Additionally, compared to LTC facilities, the DAL population studied in ACCES was found to have similarly high levels of medication use. The high degree of cognitive and mental health concerns in this setting would be expected to lead to greater dependence on AL staff for medication management. In combination with the high degree of polypharmacy in this setting, these findings suggest that a

higher degree of professional oversight is required in AL settings, particularly with respect to medication management and monitoring.

The need for increased oversight in AL facilities is further indicated by the high rates of hospitalization from these facilities. The reported rates of hospital admission from AL facilities are significantly higher than those from LTC.[112] Given that acute care hospitalizations come at a considerable cost,[139,143] measures to reduce hospitalization (related to adverse drug events, or other concerns) should be prioritized. Requirements for 24-hour oversight of AL residents by RNs or LPNs may be a valuable policy in order to improve the quality of care provided to residents and reduce costs associated with acute care hospitalizations (resulting from adverse drug events, or other quality of care concerns). Indeed, increased RN and LPN staffing per resident has been found to be associated with reductions in the number of adverse drug events in AL facilities.[121,122,132] Additional policies which may be valuable include involvement of on-staff physicians or pharmacists in the medication management of AL residents.

Although the findings of the present research are not enough to support conclusive statements or policy recommendations regarding the use of frailty measures to identify those at highest risk of adverse events related to their medication use, these findings offer sufficient evidence to support the continuation of research in this area. In order to further explore this research question, future studies should be conducted with a larger sample of participants. Since some findings were not statistically significant, larger sample sizes would allow for assessment of whether moderately elevated risks are meaningful. Such larger sample sizes would be particularly useful when considering diabetes medications as the exposure of interest. Given the relatively low proportion of residents with diabetes, findings associated with this exposure were often not significant in the present sample. Larger sample sizes may also allow the opportunity to restrict the study sample

to only those participants with a medical condition indicating the use of the medication exposure of interest. Such restriction may be more precise than model adjustment as a means of controlling for possible confounding by indication.

Another consideration for future research would be exploration of incident medication use as the exposure of interest, rather than prevalent medication use, eliminating the concern over healthy user bias. An assessment of the severity of disease that indicates the use of the medication of interest would also be a useful addition to future studies. Controlling for the severity of the disease in analyses would allow for determination of whether frailty status indicates a level of vulnerability above that captured by disease severity.

Future research may also consider the relationship between high-risk medications and adverse outcomes, as modified by frailty status, in community-dwelling older adults, or those residing in LTC. Another path for future research could be the consideration of additional outcomes which are potentially relevant to the exposure of high-risk/antipsychotic medication use, such as death, falls or decreased functional capacity.

This study did not provide any obvious conclusions regarding the best frailty measure for identifying individuals particularly vulnerable to medication-related adverse events. However, the CHS measure (with relative cut-points) and the full FI appear promising for use in future research. In particular, full FI frailty was best able to identify residents at greater risk when using antipsychotics, anticoagulants, antiplatelet agents and medications from multiple HR drug classes, while CHSrel may be particularly relevant for distinguishing risk among non-ASA antiplatelet users. When assessing frailty using these measures, researchers should utilize cut-points relevant to the study population under investigation.

7. CONCLUSIONS

The prevalence of use of high-risk (HR) medications in the ACCES designated assisted living (DAL) population was observed to be quite high with 63.3% of residents using at least one HR medication. The HR medications considered in the present study (oral anticoagulants, oral antiplatelet agents, insulin and oral antidiabetic agents) have a narrow therapeutic window in terms of dosage and timing. Outside of this window, the medications can be ineffective, or even hazardous. Indeed, it has been reported that these medication classes are responsible for the majority of medication-related hospitalizations.[30,55] Additionally, despite warnings against the use of antipsychotic agents in older adults with dementia, 35.9% of residents with dementia were observed to be using an antipsychotic agent in the ACCES DAL cohort.

Within the ACCES DAL cohort, the full FI (86-item frailty index), CHSrel (CHS frailty measure with relative cut-points) and the interRAI CHESS scale each allocated a balanced distribution of residents into the categories frail, pre-frail and robust, suggesting that each of these measures is suitable for differentiating levels of vulnerability within the vulnerable assisted living (AL) population. Additionally, frailty, as determined by each of these three measures, was found to be associated with significantly increased risk of first-event hospitalization.

Although use of HR/antipsychotic medication was not found to be associated with hospitalization risk (except in the case of non-ASA antiplatelet agents), upon stratification by frailty status, it was found that frail individuals had an increased risk of hospitalization when using antipsychotic agents (Full FI or CHSrel frailty), anticoagulants (Full FI frailty), antiplatelet agents (Full FI frailty), or medications from any of the high-risk drug classes (Full FI frailty). The risk of hospitalization among frail users of insulin or oral antidiabetic agents was not found to be significantly elevated above the risk for non-frail users. This observation may be related to

the relatively small proportion of residents with diabetes, resulting in small exposure groups for insulin and oral antidiabetic use. The significantly heightened hospitalization risks observed for frail users of the other medication classes support the hypothesis that frailty status may modify the risk associated with HR/antipsychotic medication use.

Descriptive results demonstrated potential concerns with the match between skilled care provision and frailty/medication use in AL settings by revealing that residents identified as frail by the Full FI, and residents using HR/antipsychotic medications less often resided in facilities with skilled care staff (registered nurse and/or licensed practical nurse staff, physician affiliation, pharmacist involvement) compared to non-frail residents and residents not using the medication classes of interest. These findings may indicate a need for better balance between the skilled care provision in AL facilities and the complexity of residents (in terms of medication use and frailty status).

Based on the findings of this research and the peer-reviewed literature, it is recommended that policy be introduced to dictate a minimum level of skilled medication oversight required in AL facilities, potentially based on the complexity of residents. Additionally, it is recommended that future research should be conducted to further explore the role of frailty as a predictor of adverse medication-related outcomes with larger sample sizes and the use of rigorous pharmacoepidemiologic methodology.

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APPENDICES

Appendix A: Summary of Studies Considering Frailty, Medication Use and Adverse Outcomes

Author, year	Design/ Sample/ Setting	Independent Variables	Outcome	Findings	Strengths	Limitations
Runganga, 2014[17]	-Prospective cohort study; -351 older patients receiving post-discharge transitional home care at six sites in two states of Australia; -Data collection carried out from Nov 2009 - Sept 2010	**Exposure:** Polypharmacy (5-9 drugs) Hyper-polypharmacy (≥ 10 drugs); **Frailty Measure:** 57-item Frailty Index (derived from interRAI-HC)	Failure to improve ADL or IADL,[197] or falls over the transitional care period (TCP)	-Increased level of polypharmacy was associated with reduced improvements in ADLs and IADLs, although only one OR reached statistical significance: Hyper-polypharmacy was associated with failure to improve IADLs (OR = 3.42, 95% CI = 1.13-10.38) -The polypharmacy group was most strongly associated with falls (OR = 4.69, 95% CI = 1.06 - 20.68); -Frailty status was observed to mediate the effect of polypharmacy	-Prospective data collection	-Short follow-up period (average 7 weeks); -No inclusion of possible confounders in multivariate model (despite having a great deal of data on potential confounders available from the interRAI-HC); -Few findings reached statistical significance; -Drug use determined from hospital records, no information on continued use/adherence
Pugh, 2014[15]	-Retrospective cohort study; -135,155 veterans aged 65 and older with at least 1 hospital admission between Oct 2005 and Sept 2006;	**Exposure:** Use of any HEDIS high risk medications in the elderly (HRME);[29] **Frailty Measure:** Presence of one or more of the following diagnoses (which	Hospital re-admission within 30 days of discharge	-Exposure to chronic HRME without frailty is protective over re-admission (OR = 0.87, 95% CI = 0.82-0.92) -Frail participants exposed to chronic HRME were not protected (OR = 1.08, 95% CI = 0.97-1.20; -No interaction between	-Large sample; -Consideration of both chronic and incident medication use; -Inclusion of relevant covariates (supported by existing	-Determine frailty based on diagnoses associated with frailty, rather than measuring frailty directly; -Short follow-up period (30 days); -Drug use determined from pharmacy data,

	-US National Veterans Affairs (VA) data	have been found to be associated with the CHS frailty measure in prior studies): coagulotherapy, involuntary weight loss, fluid and electrolyte imbalance, anemia, and fall or fracture		frailty-related diagnoses and *incident* HRME	literature) in multivariate model	no information on medication adherence;
Bennett, 2014[16]	-Prospective cohort study; -204 older patients (≥ 60 years) admitted to the emergency department of a Sydney, AUS tertiary referral hospital due to a fall -Data collection from June 2012 - March 2013	**Exposure:** -Use of fall-risk increasing drugs (FRIDs), -Number of medications, or -Potential drug-drug interactions (DDIs) at admission and discharge **Frailty Measure:** The Reported Edmonton Frail Scale, assessed at admission	-Recurrent falls, -Functional decline (as assessed by ADLs and IADLs),[197] -Institutional-ization (nursing home admission or rehabilitation hospital), -Rehospital-isation in the two months following index hospital admission	-Frail participants were more likely than robust to use FRIDs, high number of medications and have potential DDIs; -Number of FRIDs was associated with falls (OR = 1.7, 95% CI = 1.3-2.1), institutionalization (OR =1.3, 95% CI =1.1-1.6), and functional decline (OR = 1.3, 95% CI = 1.1-1.6); -Overall number of medications was associated with falls, hospitalization and functional decline to a lesser degree; -Potential DDIs were not found to be significantly associated with adverse outcomes; -The threshold for the number of FRIDs that predicts falls was 2.5 in the robust and 1.5 in the frail	-Prospective data collection; -Inclusion of relevant covariates (supported by existing literature) in multivariate model	-Short follow-up period (2 months); -Subjects recruited from a single hospital - limits generalizability; -Drug use determined from hospital records, no information on adherence before and after hospitalization;

Appendix B: High Risk and Antipsychotic Medications

The following table lists the specific medications included within each of the medication classes considered in the present research, along with the corresponding ATC codes

Drug Measure	Drug Name (generic)	ATC code
Any use of Oral Anticoagulant	Warfarin	B01AA03
	Acenocoumarol	B01AA07
Any use of Oral Antiplatelet	Clopidogrel	B01AC04
	Ticlopidine	B01AC05
	Dipyridamole	B01AC07
	ASA + dipyridamole	B01AC30
	ASA	N02BA01
	ASA + other combinations	N02BA51 N02BA71
	Sulfasalazine§	A07EC01
	Aminosalicylic acid, Mesalazine§	A07EC02
	Olsalazine§	A07EC03
Any Use of Oral Antidiabetic Agents	Metformin (Biguanide)	A10BA02
	Glyburide (Sulfonylurea)	A10BB01
	Gliclazide (Sulfonylurea)	A10BB09
	Acarbose (alpha-glucosidase inhibitor)	A10BF01
	Rosiglitazone (Thiazolidinedione)	A10BG02
	Pioglitazone (Thiazolidinedione)	A10BG03
	Sitagliptin (DPP-4 Inhibitor)	A10BH01
	Repaglinide (Meglitinide)	A10BX02
Any use of Insulin(s)	Insulin (human): Toronto, Novolin, Humulin R, etc.	A10AB01
	Insulin Aspart	A10AB05 A10AD05
	Insulin (human): Humulin N, Novolin NPH, etc.	A10AC01
	Insulin (human): Novolin 30/70, Humulin 30/70, etc.	A10AD01
	Insulin Glargine	A10AE04
	Insulin Detemir	A10AE05
	Insulin, not specified†	A10A
Any use of Antipsychotics	Chlorpromazine (phenothiazines)	N05AA01
	Methotrimeprazine (phenothiazines)	N05AA02
	Fluphenazine (phenothiazines)	N05AB02
	Perphenazine (phenothiazines)	N05AB03
	Prochlorperazine (phenothiazines)	N05AB04
	Trifluoperazine (phenothiazines)	N05AB06
	Haloperidol (butyrophenones)	N05AD01
	Flupentixol (thioxanthenes)	N05AF01
	Zuclopenthixol (thioxanthenes)	N05AF05
	Loxapine (misc. antipsychotic)	N05AH01
	Clozapine (atypical antipsychotic)	N05AH02
	Olanzapine (atypical)	N05AH03
	Quetiapine (atypical)	N05AH04
	Risperidone (atypical)	N05AX08

§ Sulfasalazine (and its metabolites) were included as they have been shown to have antiplatelet effects comparable to ASA

†In some instances, type of insulin was not recorded during ACCES data collection, so 4-digit ATC code was used

Appendix C: Full Frailty Index[82]

The following 86-item frailty index is based on the criteria used by Searle et al.[83] and utilizes information from the interRAI-AL. The presence of each condition adds "1" to the person's index score (unless otherwise indicated).

Name of Frailty Item by Subject Header
Psychosocial Well Being
Not close to someone in the facility
No strong supportive relationships with family
Infrequent participation in long-standing social activities
Infrequent visits from family/friends
Infrequent interaction with family/friends
Mood
Makes negative statements
Persistent anger
Unrealistic fears
Repetitive health complaints
Repetitive anxiety
Sad, pained, worried facial expressions
Crying, tearfulness
Withdrawal from activities of interest
Reduced social interactions
Lack of pleasure in life
Cognition
Minimally impaired (0.5), or moderately/severely impaired (1) decision-making skills
Short-term memory problems
Procedural memory problems
Situational memory problems
Easily distracted
Episodes of disorganized speech
Declined decision-making in last 90 days
Communication
At least some difficulty to make self understood
At least some difficulty understanding
Moderate/severe hearing problems
Moderate/severe vision problems

Functional status
Limited help (0.5), extensive help (1) with phone use
Limited help (0.5), extensive help (1) with stair climbing
Limited help (0.5), extensive help (1) with shopping
Limited help (0.5), extensive help (1) with bathing
Limited help (0.5), extensive help (1) with personal hygiene
Limited help (0.5), extensive help (1) with dressing upper body
Limited help (0.5), extensive help (1) with dressing lower body
Limited help (0.5), extensive help (1) with walking
Limited help (0.5), extensive help (1) with locomotion
Limited help (0.5), extensive help (1) with transferring
Minimal help (0.5), extensive help (1) with toilet use
Minimal help (0.5), extensive help (1) with bed mobility
Minimal help (0.5), extensive help (1) with eating
Less than 1 hour of physical activity in last 3 days
Did not go out within a 3 day period
Declined in ADL over last 90 days
Incontinence
Some (0.5), daily (1) bladder incontinence
Some (0.5), daily (1) bowel incontinence
Disease diagnosis
Hip fracture, other fractures, osteoporosis
Arthritis
Alzheimer's disease/dementia
Hemiplegia
Multiple sclerosis
Paraplegia/quadriplegia
Parkinson's disease
Stroke or CVA
Hypertension
Coronary heart disease
Congestive heart failure
COPD/Emphysema/Asthma
Cancer
Diabetes
Renal disease

	Peripheral vascular disease
	Cardiac arrhythmias
	Thyroid disease
	Anemia
	Macular Degeneration
Health conditions	
	At least 1 fall in last 30 dyas
	Balance - turning around
	Balance - dizziness
	Balance - unsteady gait
	Chest pain
	Abnormal thought process
	Delusions
	Hallucinations
	Aphasia
	Vomiting
	Non-restful sleep/insomnia
	Too much sleep
	Peripheral edema
	Shortness of breath
	Fatigue - cannot complete day-to-day activities
	Pain present
	Poor self-reported health
	Unstable health
Nutrition/Medications	
	BMI 30-40 (0.5), BMI > 40 (1)
	Weight loss 5% or more in last 30 days or 10% in last 180 days
	Ten or more medications
	Allergy to any drug

Appendix D: Armstrong Frailty Index[90]

The following 44-item frailty index is based on index used by Armstrong et al.[90] and utilizes information from the interRAI-AL. The presence of each condition adds "1" to the person's index score (unless otherwise indicated).

Name of Frailty Item by Subject Header
Mood
Persistent anger
Unrealistic fears
Repetitive health complaints
Sad, pained, worried facial expressions
Withdrawal from activities of interest
Reduced social interactions
Communication
Moderate/severe vision problems
Functional status
Limited help (0.5), extensive help (1) with meal preparation
Limited help (0.5), extensive help (1) with ordinary housework
Limited help (0.5), extensive help (1) with managing finances
Limited help (0.5), extensive help (1) with managing medications
Limited help (0.5), extensive help (1) with stair climbing
Limited help (0.5), extensive help (1) with shopping
Limited help (0.5), extensive help (1) with bathing
Limited help (0.5), extensive help (1) with personal hygiene
Limited help (0.5), extensive help (1) with dressing upper body
Limited help (0.5), extensive help (1) with dressing lower body
Limited help (0.5), extensive help (1) with locomotion
Limited help (0.5), extensive help (1) with transferring
Minimal help (0.5), extensive help (1) with toilet use
Minimal help (0.5), extensive help (1) with eating
Incontinence
Some (0.5), daily (1) bladder incontinence
Some (0.5), daily (1) bowel incontinence
Disease diagnosis
Hip fracture, other fractures, osteoporosis
Arthritis
Alzheimer's disease/dementia

	Hemiplegia
	Multiple sclerosis
	Parkinson’s disease
	Stroke or CVA
	Hypertension
	Coronary heart disease
	Congestive heart failure
	COPD/Emphysema/Asthma
	Diabetes
	Renal disease
	Peripheral vascular disease
	Cardiac arrhythmias
	Thyroid disease
Health conditions	
	Balance - unsteady gait
	Poor self-reported health
	Unstable health
Nutrition/Medications	
	BMI 30-40 (0.5), BMI > 40 (1)
	Weight loss 5% or more in last 30 days or 10% in last 180 days

Appendix E: CHS Frailty Assessment† (CHSabs and CHSrel)

The following represents the criteria used in order to assess frailty, according to the CHS model with absolute cut-points (CHSabs) and relative cut-points (CHSrel). Frailty cut-points identify residents with the poorest scores relative to the cohort, as outlined by Freiheit, et al.[123] These criteria utilize data from the interRAI-AL as well as supplemental physical measures added to the resident assessment.

Criterion	Measure	CHSabs*	CHSrel$^{\phi}$
Slow gait	Determined by taking the better of two timed 3-meter walks.	≥7 seconds, men ≤ 173 cm; ≥ 7 seconds, women ≤ 159 cm; ≥ 6 seconds, men > 173 cm; ≥ 6 seconds, women > 159 cm	Slowest quartile of walk times: > 9 seconds, men; > 10 seconds, women
Muscle weaknesses	Average of three grip strength readings using a handheld dynamometer.$^{\Upsilon}$	BMI-specific thresholds: ≤ 29-32 kg, men; ≤ 17-21 kg, women	Lowest quartile of grip-strength readings: < 15 kg, men; < 7 kg, women
Low physical activity	Reported minutes over two weeks per activity type - from the interRAI-AL "Exercise or Leisure Activities"§	Activities were mapped to Minnesota Leisure Time Activity Questionnaire.[198] Kcals per week calculated based on the intensity codes: < 383 Kcals/week, men; < 270 Kcals/week, women	< 140 minutes/two weeks (< 10 minutes/day on average) ‖
Unintentional weight loss	Answer to question: "In the past year have you lost more than 10 pounds unintentionally"¶	Response of "yes"	Response of "yes"
Exhaustion	Answers to 3 questions: "In the past month, on average, have you been: 1) Feeling unusually tired during the day?; 2) Feeling unusually weak?; and/or, 3) Feeling an unusually low energy level?"ǂ	Response of "yes" to any of the 3 questions	Response of "yes" to any of the 3 questions

Abbreviations: CHS = Cardiovascular Health Study, AL = assisted living, cm = centimeters, BMI = body mass index, kg = kilograms, kcals = kilocalories.

†Based on the measure detailed in Fried, 2001.[80]

*CHSabs frailty assessed with CHS-specified absolute cut-points.[80]

ϕ CHSrel frailty assessed with DAL-population based relative cut-points (identified the poorest scores in the cohort) as defined by Freiheit, et al.[123]

ϒ JAMAR®, Sammons Preston Rolyan, Bolingbrook, IL.

§Include: aquasize/swimming; bowling; dancing; exercise bike/treadmill; exercise program; floor curling/lawn bowling; gardening; household chores; shuffleboard/pool; Tai chi/yoga; walking/wheeling indoors & outdoors.

¶CHS also allowed actual unintentional 5% weight loss over 1-year (not assessed in ACCES).

ǂ CHS used 2 items from the CES-D Scale [35]: "I feel that everything I do is an effort" and "I cannot get going" (those reporting feeling this way at least 3–4 days/previous week fulfilled the criterion).

Appendix F: CHESS Scale[88]

The CHESS scale offers a measure of health instability. The score is derived from interRAI assessments and can range from 0 to 5, with 0 representing stability and 5 representing unstable health. The following criteria are used to determine CHESS score with the score for each item shown in brackets.

Symptoms (No symptoms = 0 ;1 symptom present = 1 ; 2+ symptoms present = 2)
Vomiting
Dehydration (insufficient fluid)*
Decline in fluid/food intake*
Weight loss
Shortness of breath
Edema
Worsening of decision making over previous 90 days (1)
Decline in activities of daily living over past 90 days (1)
End-stage disease (1)

*Two of the items from the CHESS scale were not included in the interRAI-AL, and thus, cannot be used for the calculation of the CHESS score in the proposed research

Appendix G: Diagnoses associated with the Use of High-Risk / Antipsychotic Medication and Associations with Frailty Status

Table a. Baseline Distribution of Diagnoses Related to High-Risk / Antipsychotic Medication Use by Frailty Status [CHSrel Frailty Measure] among DAL Residents

	Total	CHSrel Frailty; % of column total (n)			
	% (n)	Robust	Pre-Frail	Frail	p-value
Overall	946	25.8 (244)	55.0 (520)	19.2 (182)	
Diagnoses Related to Anticoagulant Use ϕ					
No diagnoses related to anticoagulant use	42.9 (406)	50.8 (124)	43.1 (224)	31.9 (58)	0.0005
1+ diagnoses related to anticoagulant use	57.1 (540)	49.2 (120)	56.9 (296)	68.1 (124)	
Diagnoses Related to Oral Antiplatelet Use ¶					
No diagnoses related to antiplatelet use	22.1 (209)	24.6 (60)	22.5 (117)	17.6 (32)	0.2138
1+ diagnoses related to antiplatelet use	77.9 (737)	75.4 (184)	77.5 (403)	82.4 (150)	
Diagnoses Related to Oral Antidiabetic Use Ɏ					
No diagnoses related to oral antidiabetic use	23.2 (220)	26.2 (64)	24.2 (126)	16.5 (30)	0.0459
1+ diagnoses related to oral antidiabetic use	76.7 (726)	73.8 (180)	75.8 (394)	83.5 (152)	
Diagnoses Related to Insulin Use †					
No diagnoses related to insulin use	23.9 (226)	25.8 (63)	24.6 (128)	19.2 (35)	0.2438
1+ diagnoses related to insulin use	76.1 (720)	74.2 (181)	75.4 (392)	80.8 (147)	
Diagnoses Related to Insulin/Sulfonylurea Use Ɏǁ					
No diagnoses related to insulin or sulfonylurea use	19.5 (184)	21.7 (53)	20.8 (108)	12.6 (23)	0.0338
1+ diagnoses related to insulin and/or sulfonylurea use	80.5 (762)	78.3 (191)	79.2 (412)	87.4 (159)	
Diagnoses Related to any Diabetic Drug Use Ɏǁ					
No diagnoses related to insulin or oral antidiabetic use	19.5 (184)	21.7 (53)	20.8 (108)	12.6 (23)	0.0338
1+ diagnoses related to insulin and/or oral antidiabetic use	80.5 (762)	78.3 (191)	79.2 (412)	87.4 (159)	
Diagnoses Related to High-risk Medication Use ϕ¶ Ɏǁ					
No diagnoses related to use of any of the 4 HR drug classes	15.0 (142)	17.6 (43)	15.4 (80)	10.4 (19)	0.1140
1+ diagnoses related to HR drug use	85.0 (804)	82.4 (201)	84.6 (440)	89.6 (163)	
Diagnoses Related to Antipsychotic Drug Use *					
No diagnoses related to antipsychotic use	25.7 (243)	21.7 (53)	27.7 (144)	25.3 (46)	0.210
1+ diagnoses related to antipsychotic use	74.3 (703)	78.3 (191)	72.3 (376)	74.7 (136)	

Abbreviations: DAL=Designated Assisted Living; CHSrel=Cardiovascular Health Study Frailty Measure (relative cut-points)
ϕ Diagnoses related to oral anticoagulant use included stroke, coronary heart disease, congestive heart failure, cardiac dysrhythmias, venous disorders (deep vein thrombosis, chronic venous insufficiency, pulmonary embolism, superficial venous thrombosis or phlebitis, varicose veins).
¶ Diagnoses related to oral antiplatelet use included stroke, hypertension, coronary heart disease, diabetes, lipid abnormality.
Ɏ Diagnoses related to oral antidiabetic use included diabetes, congestive heart failure, lipid abnormality, hypertension, coronary heart disease.
ǁ Diagnoses related to insulin use included diabetes, congestive heart failure, hypertension, chronic obstructive pulmonary disease
* Diagnoses related to antipsychotic use included dementia, schizophrenia, anxiety, depression.

Table b. Baseline Distribution of Diagnoses Related to High-Risk / Antipsychotic Medication Use by Frailty Status [Full FI Frailty Measure] among DAL Residents

	Total % (n)	Full FI Frailty; % of column total (n)			p-value
		Robust	Pre-Frail	Frail	
Overall	1089	33.6 (366)	38.9 (424)	27.5 (299)	
Diagnoses Related to Anticoagulant Use ϕ					
No diagnoses related to anticoagulant use	55.8 (608)	46.7 (195)	41.5 (176)	36.8 (110)	< 0.0001
1+ diagnoses related to anticoagulant use	44.2 (481)	53.3 (171)	58.5 (248)	63.2 (189)	
Diagnoses Related to Oral Antiplatelet Use ¶					
No diagnoses related to antiplatelet use	22.8 (52)	29.5 (108)	20.7 (88)	17.4 (52)	0.0005
1+ diagnoses related to antiplatelet use	77.2 (841)	70.5 (258)	79.3 (336)	82.6 (247)	
Diagnoses Related to Oral Antidiabetic Use Ɣ					
No diagnoses related to oral antidiabetic use	23.9 (260)	32.5 (119)	20.8 (88)	17.7 (53)	<0.0001
1+ diagnoses related to oral antidiabetic use	76.1 (829)	67.5 (247)	79.2 (336)	82.3 (246)	
Diagnoses Related to Insulin Use ǁ					
No diagnoses related to insulin use	24.5 (267)	30.9 (113)	22.9 (97)	19.1 (57)	0.0012
1+ diagnoses related to insulin use	75.5 (822)	69.1 (253)	77.1 (327)	80.9 (242)	
Diagnoses Related to Insulin/Sulfonylurea Use Ɣǁ					
No diagnoses related to insulin or sulfonylurea use	20.0 (218)	27.1 (99)	17.5 (74)	15.1 (45)	0.0001
1+ diagnoses related to insulin and/or sulfonylurea use	80.0 (871)	72.9 (267)	82.5 (350)	84.9 (254)	
Diagnoses Related to any Diabetic Drug Use Ɣǁ					
No diagnoses related to insulin or oral antidiabetic use	20.0 (218)	27.1 (99)	17.5 (74)	15.1 (45)	0.0001
1+ diagnoses related to insulin and/or oral antidiabetic use	80.0 (871)	72.9 (267)	82.5 (350)	84.9 (254)	
Diagnoses Related to High-risk Medication Use ϕ¶ Ɣǁ					
No diagnoses related to use of any of the 4 HR drug classes	15.7 (171)	20.5 (75)	13.9 (59)	12.4 (37)	0.0072
1+ diagnoses related to HR drug use	84.3 (918)	79.5 (291)	86.1 (365)	87.6 (262)	
Diagnoses Related to Antipsychotic Drug Use *					
No diagnoses related to antipsychotic use	24.4 (266)	37.2 (136)	25.2 (107)	7.7 (23)	<0.0001
1+ diagnoses related to antipsychotic use	75.6 (823)	62.8 (230)	74.8 (317)	92.3 (276)	

Abbreviations: DAL=Designated Assisted Living; Full FI= Full (86-item) Frailty Index

ϕ Diagnoses related to oral anticoagulant use included stroke, coronary heart disease, congestive heart failure, cardiac dysrhythmias, venous disorders (deep vein thrombosis, chronic venous insufficiency, pulmonary embolism, superficial venous thrombosis or phlebitis, varicose veins).

¶ Diagnoses related to oral antiplatelet use included stroke, hypertension, coronary heart disease, diabetes, lipid abnormality.

Ɣ Diagnoses related to oral antidiabetic use included diabetes, congestive heart failure, lipid abnormality, hypertension, coronary heart disease.

ǁ Diagnoses related to insulin use included diabetes, congestive heart failure, hypertension, chronic obstructive pulmonary disease

* Diagnoses related to antipsychotic use included dementia, schizophrenia, anxiety, depression.

Table c. Baseline Distribution of Diagnoses Related to High-Risk / Antipsychotic Medication Use by Frailty Status [CHESS Frailty Measure] among DAL Residents

	Total % (n)	CHESS Frailty; % of column total (n)			p-value
		Robust	Pre-Frail	Frail	
Overall	1089	46.2 (503)	29.4 (320)	24.4 (266)	
Diagnoses Related to Anticoagulant Use ϕ					
No diagnoses related to anticoagulant use	44.2 (481)	48.3 (243)	40.6 (130)	40.6 (108)	0.0388
1+ diagnoses related to anticoagulant use	55.8 (608)	51.7 (260)	59.4 (190)	59.4 (158)	
Diagnoses Related to Oral Antiplatelet Use ¶					
No diagnoses related to antiplatelet use	22.8 (248)	23.7 (119)	24.4 (78)	19.2 (51)	0.2656
1+ diagnoses related to antiplatelet use	77.2 (841)	76.3 (384)	75.6 (242)	80.8 (215)	
Diagnoses Related to Oral Antidiabetic Use Ɣ					
No diagnoses related to oral antidiabetic use	23.9 (260)	27.0 (136)	23.4 (75)	18.4 (49)	0.0279
1+ diagnoses related to oral antidiabetic use	76.1 (829)	73.0 (367)	76.6 (245)	81.6 (217)	
Diagnoses Related to Insulin Use ǁ					
No diagnoses related to insulin use	24.5 (267)	27.0 (136)	23.4 (75)	21.1 (56)	0.1609
1+ diagnoses related to insulin use	75.5 (822)	73.0 (367)	76.6 (245)	78.9 (210)	
Diagnoses Related to Insulin/Sulfonylurea Use Ɣǁ					
No diagnoses related to insulin or sulfonylurea use	20.0 (218)	23.3 (117)	19.1 (61)	15.0 (40)	0.0223
1+ diagnoses related to insulin and/or sulfonylurea use	80.0 (871)	76.7 (386)	80.9 (259)	85.0 (226)	
Diagnoses Related to any Diabetic Drug Use Ɣǁ					
No diagnoses related to insulin or oral antidiabetic use	20.0 (218)	23.3 (117)	19.1 (61)	15.0 (40)	0.0223
1+ diagnoses related to insulin and/or oral antidiabetic use	80.0 (871)	76.7 (386)	80.9 (259)	85.0 (226)	
Diagnoses Related to High-risk Medication Use ϕ¶ Ɣǁ					
No diagnoses related to use of any of the 4 HR drug classes	15.7 (171)	17.3 (87)	15.6 (50)	12.8 (34)	0.2618
1+ diagnoses related to HR drug use	84.3 (918)	82.7 (416)	84.4 (270)	87.2 (232)	
Diagnoses Related to Antipsychotic Drug Use *					
No diagnoses related to antipsychotic use	24.4 (266)	23.5 (118)	30.3 (97)	19.2 (51)	0.0060
1+ diagnoses related to antipsychotic use	75.6 (823)	76.5 (385)	69.7 (223)	80.8 (215)	

Abbreviations: DAL=Designated Assisted Living; CHESS= Changes in Health, End-stage disease and Signs and Symptoms of medical problems scale

ϕ Diagnoses related to oral anticoagulant use included stroke, coronary heart disease, congestive heart failure, cardiac dysrhythmias, venous disorders (deep vein thrombosis, chronic venous insufficiency, pulmonary embolism, superficial venous thrombosis or phlebitis, varicose veins).

¶ Diagnoses related to oral antiplatelet use included stroke, hypertension, coronary heart disease, diabetes, lipid abnormality.

Ɣ Diagnoses related to oral antidiabetic use included diabetes, congestive heart failure, lipid abnormality, hypertension, coronary heart disease.

ǁ Diagnoses related to insulin use included diabetes, congestive heart failure, hypertension, chronic obstructive pulmonary disease

* Diagnoses related to antipsychotic use included dementia, schizophrenia, anxiety, depression.

Appendix H: Baseline Characteristics of ACCES DAL (n=1,066) and LTC (n=976) Residents (From Hogan, 2014)[112]

		DAL* n (% of total)	LTC† n (% of total)	p-value
		n=1066	n=976	
Sociodemographic Characteristics & Social Wellbeing				
Age	mean ±SD	84.9±7.3	85.4±7.6	0.1163
	65-79	268 (25.1)	226 (23.2)	0.2672
	80-85	280 (26.3)	251 (25.7)	
	86-89	243 (22.8)	210 (21.5)	
	90+	275 (25.8)	289 (29.6)	
Sex	Female	818 (76.7)	641 (65.7)	<0.001
	Male	248 (23.3)	335 (34.2)	
Marital Status				<0.001
	Widowed	761 (71.4)	573 (58.7)	
	Married / Partner	156 (14.6)	246 (25.2)	
	Never married / separated / divorced	149 (14.0)	157 (16.1)	
Strength of Social Relationships‡				<0.001
	Moderate/High (3-5)	873 (81.9)	641 (65.7)	
	Low/None (0-2)	193 (18.1)	335 (34.3)	
Avg Time Involved in Activities§				<0.001
	Most (>2/3 time)	157 (14.7)	105 (10.8)	
	Some (1/3 to 2/3 time)	417 (39.1)	326 (33.4)	
	Little-None (<1/3 time)	492 (46.2)	544 (55.8)	
Health & Functional Status				
Cognition (CPS Score)				<0.001
	Intact (0)	223 (20.9)	60 (6.2)	
	Borderline Intact (1)	211 (19.8)	93 (9.5)	
	Mild Impairment (2)	336 (31.5)	252 (25.9)	
	Mod-Severe-Very Severe Impairment (3+)	296 (27.8)	570 (58.5)	
Activities of Daily Living (ADL score)				<0.001
	Independent (0)	454 (42.6)	50 (5.1)	
	Supervision Required (1)	186 (17.5)	50 (5.1)	
	Limited Impairment (2)	126 (11.8)	81 (8.3)	
	Extensive Assistance Req'd/Dependent (3+)	300 (28.1)	795 (81.5)	
Health Instability (CHESS score)¶				0.0067
	Stable (0)	496 (46.5)	382 (39.1)	
	Mild (1)	312 (29.3)	335 (34.3)	
	Mild-Moderate (2)	184 (17.3)	192 (19.7)	
	Moderate-High (3+)	74 (6.9)	67 (6.9)	

	DAL* n (% of total)	LTC† n (% of total)	p-value
	n=1066	n=976	
Fatigue, <3 days			<0.001
None	433 (40.6)	387 (39.7)	
Minimal	461 (43.3)	318 (32.6)	
Moderate-Severe	172 (16.1)	271 (27.8)	
Primary Mode Locomotion			<0.001
Walks independently	227 (21.3)	88 (9.0)	
Walks with Assistive Device	625 (58.6)	205 (21.0)	
Wheelchair/Scooter**	214 (20.0)	683 (70.0)	
Falls CAP			0.4016
1+ Falls / 90 days	305 (28.6)	263 (27.0)	
None	761 (71.4)	713 (73.1)	
Depressive Symptoms (DRS Score)			<0.001
Yes (3+)	203 (19.0)	495 (50.9)	
No (<3)	863 (81.0)	478 (49.1)	
Aggressive Behaviour (ABS Score)††			<0.001
None (0)	760 (71.3)	334 (34.2)	
Moderate (1-2)	174 (16.3)	197 (20.2)	
Severe (3-5)	102 (9.6)	223 (22.9)	
Very Severe (6+)	30 (2.8)	222 (22.8)	
# Chronic Conditions			
mean ±SD	4.7±2.0	5.2±2.1	<0.001
0-3	323 (30.3)	199 (20.4)	<0.001
4-5	398 (37.3)	370 (37.9)	
6+	345 (32.4)	407 (41.7)	
# Medications			
mean ±SD	8.3 ±3.7	7.9±3.7	0.0147
0-6	349 (32.7)	351 (36.0)	0.4593
7-8	232 (21.8)	209 (21.4)	
9-10	214 (20.1)	187 (19.2)	
11+	271 (25.4)	229 (23.5)	
Adv Directive – Do Not Hospitalize			<0.001
Yes	109 (10.2)	290 (29.7)	
No	957 (89.8)	686 (70.3)	
Previous Inpatient Hospitalizations (prior year)			<0.001
0	663 (62.2)	737 (75.5)	
1	254 (23.8)	156 (16.0)	
2+	149 (14.0)	83 (8.5)	
Bladder Incontinence			<0.001
Continent	436 (40.9)	93 (9.5)	
Some control, infrequent episodes	156 (14.6)	112 (11.5)	
Occasional incontinence	114 (10.7)	96 (9.8)	
Frequent episodes, no control	360 (33.8)	675 (69.2)	

		DAL* n (% of total)	LTC† n (% of total)	p-value
		n=1066	n=976	
Bowel Incontinence				<0.001
	Continent	766 (71.9)	303 (31.1)	
	Some control, infrequent episodes	165 (15.5)	164 (16.8)	
	Occasional incontinence	83 (7.8)	143 (14.7)	
	Frequent episodes, no control	52 (4.9)	366 (37.5)	
System / Facility Factors				
Region	1 (urban)	311 (29.2)	296 (30.3)	0.7637
	2 (mixed urban/rural)	228 (21.4)	204 (20.9)	
	3 (rural)	153 (14.4)	143 (14.7)	
	4 (urban)	268 (25.1)	225 (23.1)	
	5 (rural)	106 (9.9)	108 (11.1)	
Ownership				<0.001
	For-profit	420 (39.4)	278 (28.5)	
	Not-for-profit/RHA	646 (60.6)	698 (71.5)	
Part of Chain				<0.001
	No / RHA operated	157 (14.7)	337 (34.5)	
	Yes – AL (LTC) Chain only	334 (31.3)	315 (32.3)	
	Yes – AL & LTC Chain	575 (53.9)	324 (33.2)	
Year DAL (LTC) Spaces Opened‡‡				<0.001
	<2002	273 (25.6)	866 (94.0)	
	2002-03	362 (34.0)	39 (4.2)	
	2004+	431 (40.4)	16 (1.7)	
#DAL (LTC) Spaces				<0.001
	mean ±SD	44±26	131±107	
	median	38	100	
	IQR	27-50	56-188	
#Total Spaces				0.0271
	mean±SD	140±110	151±116	
	median	112	120	
	IQR	65-154	83-194	
Levels of Care on Site§§				0.6643
	DAL (LTC) only / DAL (LTC) + Equivalent/Lower	859 (80.6)	779 (79.8)	
	DAL (LTC) + Higher Level	207 (19.4)	197 (20.2)	
LTC Beds On Site				
	No	865 (81.1)	--	
	Yes (LTC/LTC-dem)	201 (18.9)	--	
LPN/RN Coverage on Site				
	Neither on site	295 (27.7)		
	LPN &/or RN <24/7	108 (10.1)		
	LPN &/or RN 24/7	663 (62.2)	976 (100.0)	

	DAL* n (% of total)	LTC† n (% of total)	p-value
	n=1066	n=976	
Physician (GP) Affiliated with Site			<0.001
No	687 (64.5)	17 (1.7)	
Yes, office on site	169 (15.9)	261 (26.7)	
Yes, no office on site	210 (19.7)	698 (71.5)	
Community Size			<0.001
<10,000	222 (20.8)	325 (33.3)	
10,000-99,999	292 (27.4)	196 (20.1)	
1 million+	552 (51.8)	455 (46.6)	

Abbreviations: ACCES=Alberta Continuing Care Epidemiological Studies; DAL=designated assisted living; SD=standard deviation.

* DAL sample excludes 3 residents with unknown outcome and 20 residents who declined consent for data linkage.

† LTC sample excludes 3 residents who could not be linked with administrative data and 21 residents who declined consent for data linkage.

‡ Social relationships based on summary score of items assessing whether resident is close to someone in the facility, has a strong/supportive relationship with family, participates in social activities of longstanding interest and visits/has other interactions with longstanding social relation/family member (in past week).

§ Activity involvement reflects when awake and not receiving treatments or ADL care.

¶ 2 items (insufficient fluid, noticeable decline in food/fluid) used to calculate CHESS are not included on interRAI-AL tool.

** Includes 1 DAL resident and 9 LTC residents who were bedbound.

†† ABS is a summary scale of 4 behaviours (verbal abuse, physical abuse, socially inappropriate or disruptive, resists care) with higher scores indicating a greater number and frequency of behavioural issues.

‡‡ For LTC, 55 residents have missing value for year LTC facility opened.

§§ For DAL facilities: Equivalent level of care (private AL, residential, respite [not in LTC], community support & transition beds); Lower level of care (independent living, lodge, condo); Higher level of care (LTC [including respite], acute care); For LTC facilities: Equivalent level of care (other LTC bed types); Lower level of care (DAL, private AL, residential, respite [not in LTC], community support & transition beds, independent living, lodge, condo); Higher level of care (acute care).

Appendix I: Most Common Causes for Hospitalization* among DAL residents (From Hogan, et al.)[112]

Category (Most Responsible Diagnosis)	**DAL Resident Hospitalization**		
	n	% all hospitalizations (n=413)	% of residents (n=1066)
Infectious Diseases			
Septicemia	5	1.2%	0.5%
Respiratory	27	6.5%	2.5%
Urinary	20	4.8%	1.9%
Other	10	2.4%	0.9%
Total	**62**	**15.0%**	**5.8%**
Injuries			
Hip Fracture	22	5.3%	2.1%
Other Fracture	26	6.3%	2.4%
Other Injuries	6	1.5%	0.6%
Total	**54**	**13.1%**	**5.1%**
Heart Failure	28	6.8%	2.6%
Exacerbation of COPD	22	5.3%	2.1%
Cognitive Impairment			
Dementia	20	4.8%	1.9%
Delirium	2	0.5%	0.2%
Total	**22**	**5.3%**	**2.1%**
Malignant Diseases (includes Palliative Care & Pain Management)	21	5.1%	2.0%
Cerebrovascular Disease	17	4.1%	1.6%
Ischemic Heart Disease	15	3.6%	1.4%

* derived from ICD10CA codes listed for the most responsible discharge diagnosis