DETERMINANTS OF DEPRESSIVE SYMPTOM TRAJECTORIES AMONG OLDER ADULTS IN COMMUNITY AND TREATMENT SETTINGS

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ABSTRACT

Sub-diagnostic depression, sleep, and circadian rest-activity rhythm (CAR) syndromes are common in late-life, but their characteristics, prevalence, and relations to future depression are unclear. We characterized commonly occurring sleep, CAR, and depressive sign/symptom patterns using a data-driven approach applied to a large population-based study of older men. We next examined relationships of these baseline syndromes with longitudinal change in depressive symptoms. Common (32.44%) probable depressive syndromes were characterized by somatic/apathy symptoms; two subset (5.74% and 8.45%) characterized by somatic/apathy symptoms also reported emotional-related impairment. Subjective complaints without objectively (actigraph) assessed disturbances characterized two distinct classes of men (totaling 37.46%); a pattern of objective disturbance (including greater sleep fragmentation with probable prolonged sleep latency or short (<5 hour) sleep duration) occurred in both the presence (8.87%) and absence (8.51%) of subjective complaints. Only 32.18% appeared to be free of a non-normative CAR parameter; 8 classes were distinguished by activity timing, levels, and the active period length. Baseline sleep and depression latent classes were not meaningfully associated with rates of change in depression severity. The rate of increase in depressive symptoms was higher for classes with later activity and for a class with dampened, earlier, and compressed activity combined. Future work should assess the modifiability of the identified markers of depressive

symptom increases through preventive interventions. Nevertheless, there remains a need to understand mechanisms of variability in pharmacological treatment response among older adults with major depressive disorder (MDD). We therefore assessed prognostic factors associated with distinct trajectories of depressive symptom change over 12-weeks of open-label MDD treatment (with Venlafaxine XR). Only 44.59% exhibited a clear response, and the clinical prognostic factors linked to unique patterns of non-response included: worse depressive severity, longer illness duration, higher levels of guilt, worse work/activity impairment, and worse list recognition performance. Overall, this work has public health relevance by providing a novel description of common sleep-wake/depressive syndromes in the community and distinct symptom trajectories found in response to pharmacologic treatment. There is a need to integrate the identified prognostic markers with neurobiological research towards a valid predictive science of depression pathogenesis, prevention, and treatment.

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PREFACE

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1.0 INTRODUCTION

According to the World Health Organization, depressive disorders are the leading cause of disease burden in the developed world and the third leading cause globally [1]. The burden of mental illnesses, along with other non-communicable diseases, is expected to rise following the epidemiologic transition [2] which is now well underway around the globe. Major depressive disorder (MDD) entails functional impairment which often spans across settings causing significant interpersonal strain extending the burden of depression well beyond individual patients.

On the societal level depression leads to substantial lost productivity and increased health care costs [3] totaling to an estimated 83.1 billion dollars in year 2000 for the United States alone [4]. When combined with common chronic diseases, depression reduces quality of life in a synergistic manner [5]. Because depressive disorders also increase mortality [6] and cardiovascular risk [7], preventing and/or effectively treating depression is an important public health priority with far reaching social and economic implications.

For older adults, the public health imperative is not only pressing, it is also increasing. The global population aged 65 years or older is expected to double by 2040 [8]. In the United States, as the post-World War II (WWII) “baby boom” generation enters later life in unprecedented numbers, they carry with them higher rates of prior lifetime episodes of MDD [9].

Because a history of MDD is a significant risk factor for future episodes [10], it is expected that the prevalence of MDD among older adults will rise in coming decades.

Mental health problems are a strong risk factor for suicide completion [11], a problem that is especially pronounced among older men (see Center for Disease Control (CDC) statistics, Figure 1). Currently, a substantial portion (8-16%) of older adults suffer from clinically significant depressive syndromes [12]; and the geriatric mental health care system must be prepared to provide services for a growing population of older adults at risk for suicide. The burden of late-life depression is therefore an increasingly significant public health problem with already great costs including troubling, unacceptably high rates of suicide.

Further, mood disturbances do not occur in isolation and are often accompanied by other health issues like cognitive impairment, sleep disturbances, and anxiety disorders. Sleep disturbances are extremely common in older adults with depressive symptoms; for example, in the Osteoporotic Fractures in Men Sleep Study (MrOS Sleep), over 74% of older adults with clinically significant depressive symptoms also report disturbed sleep. Sleep disturbances may actually increase the risk of developing depression (for an early report, see [13]). Cognitive impairment can entail or "mimic" a depressive syndrome, while MDD increases the risk of developing cognitive impairment [14]. Altogether, among older adults the importance of effectively preventing and/or treating depression extends well beyond the realm of mood alone and most generally includes the maintenance of mental health and quality of life.

We begin by reviewing the history of psychiatric classification. Current measurement techniques and heterogeneity within late-life depression is then discussed. After addressing the prevalence and incidence of depression across the life-course, we briefly discuss risk relations in later life with a particular focus on the potentially central role of sleep-wakefulness patterns. We

conclude that a person-centered longitudinal approach is needed to understand the etiology and treatment of late-life depression.

1.1.1 History of psychiatric classification

Marking what might be considered the first official attempt to classify the burden of psychiatric conditions, in 1840 the U.S. census recorded the frequency of "idiocy/insanity" [15]. The 1880 census classification expanded to eight categories: mania, melancholia, monomania, paresis, dementia, dipsomania, and epilepsy. In 1917 the American Medico-Psychological Association and National Commission on Mental Hygiene developed a system of nomenclature for characterizing patients in mental hospitals.

Around WWII, in a leap forward described previously by Wilson [16] and the American Psychiatric Association (APA) [15], psychiatry moved out of psychiatric hospitals and into an outpatient setting. Various mental conditions related to WWII (including trauma related stress syndromes) provided a concrete picture of mental illness within the context of what Karl Menninger called the "personality-environment" struggle [17]. This psychodynamic and psychosocial framework did not clearly demarcate mental health from illness: exposed to severe trauma or an otherwise noxious environment, mental illness could emerge in anyone. Psychic conflict was the source of mental disease and the cause of disintegrating interpersonal and social contexts. The job of the psychiatrist was to thus formulate how an individual's psychosocial history and current circumstances led to the presenting symptoms. As put by Karl Menninger, "what is behind the symptom?"

Following contemporary psychoanalytic thinking, in 1952 the Diagnostic and Statistical Manual: Mental Disorders (DSM-I) was published. The DSM-I expanded the concept of

neuroticism and also included psychotic, somatization, and character disorders. This DSM version prominently referred to “reactions,” as in Adolf Meyer’s formulation of mental disorders as personal response to psychosocial circumstances. In an update published in 1968 (the DSM-II) the term “reactions” was removed although nomenclature remained both theoretical and descriptive. This set of diagnostic guidelines included vignettes illustrative of possible clinical presentations, but avoided precise disorder definitions because it was thought that symptoms were merely overt, indirect manifestations of the underlying causal conflicts [16].

Throughout the 1970’s the imminent implications of psychiatry’s newfound place within the public’s view were being borne out. At least two mounting problems threatened the established psychiatric enterprise. Ideas that psychiatry arbitrarily distinguished between well-being and illness spread alongside social and cultural change. Critics argued that psychiatry was pathologizing normal human emotions and individual differences. Public protests urged the removal of homosexuality which was included in the DSM until 1973 [18].

Meanwhile within the field, simultaneous technological advancements, a growing emphasis on biological mechanisms, and a scarcity of research funding motivated psychiatrists to embrace a more reliable, explicit classification schema within a remedicalized framework. Using early DSM versions, agreement between psychiatrist’s diagnoses of the same patient was only slightly better than chance [16]. National Institute for Mental Health funding decreased by 5% a year between 1965-1972. Improving psychiatric classification could also provide scaffolding from which to investigate the causal biological aspects within the now dominate *bio*psychosocial model. The DSM-III was therefore developed with an emphasis on assessment and diagnosis. Personified in the 1976 resignation of a psychoanalyst from the DSM-III task force, the once dominant psychoanalytic paradigm had fallen out of favor.

Empirical studies were conducted to support disorder classifications schemes, which were formed into explicit diagnostic criteria in the 1980 publication of DSM-III. This version shifted away from any particular theoretical framework and included specific lists of observable criteria for each of an expanding disorder set. As new evidence emerged and issues with the DSM-III became clear, updates were published in 1994 (the DSM-IV) and 2000 (the DSM-IV-Text Revision).

Psychoanalytic thinking formed the basis from which psychiatry evolved into the modern era. This psychodynamic tradition sought to understand the person's psychosocial history and context in order to formulate then resolve the individual patient's psychologically seeded dysfunction. To date, reliable systems of psychiatric classification have resulted in several national and community-based research studies that vastly increased our understanding of the burden and etiology of mental disease. This storied history of psychiatric classification forms the basis of the vast and ever-advancing knowledge base from which to understand the biopsychosocial causes of mental disease. Future endeavors to examine the burden and causes of mental illness will benefit from remembering the purpose of psychiatric classification in its historical context, as well once prominent theoretical dispositions which have now fallen to the wayside.

1.1.2 Current classification system and etiological research

The recent release of DSM-5 continued the incremental refinement of a descriptive medical classification system. From the re-medicalization of psychiatric classification in the DSM-III onward, the debate continued regarding how to account for both the continuous and categorical aspects of mental disorders. Critics still argue against discrete and absolute

distinctions between mental health and illness; although DSM-type systems are necessary for clinical practice and research, alone, they may be insufficient towards understanding the causal origins of mental illness.

Indeed, depressive syndromes are much more common than MDD among older adults [12], however the clinical significance of these syndromes is not clearly agreed upon. Modern thinking places mental traits on a continuum while still recognizing that beyond a certain threshold (of severity, duration, or impairment), true and burdensome pathology deserves clinical attention. The recent emphasis on explicit, atheoretical classification has led to an increase in the reliability of psychiatric diagnoses. However the search for the causal origins of mental illness also requires a high level of diagnostic validity.

In other words, etiologically useful phenotypes are those that relate homogeneously to a central disease process and/or a common causal mechanism. While the DSM-5 as well as prior versions included a system for coding severity *within* disorders, established nosology allows for within-disorder heterogeneity above and beyond a function of severity. Any of 227 possible combinations of symptoms may lead to an MDD diagnosis [19]. For the same reasons that research seeking to identify the causes of the flu would be hindered by misclassifying a hangover as influenza, it is necessary for psychiatric outcome classifications to be highly specific.

Three MDD symptoms (Table 1) are actually compound psychophysiological indicators: appetite/weight disturbance, sleep disturbance, and psychomotor disturbance. Sleep disturbance is included as one of the nine MDD symptoms, but endorsement of this single sleep symptom encompasses conditions (insomnia or hypersomnia) that result from separate causal processes. On the other hand, multiple disorders or aspects of disorders can co-occur. For example, sleep

disturbances and depression often co-occur among older adults (i.e. [20]), and this suggests a shared dysfunction and a common causal mechanism for study.

In 2011, the National Institute of Mental Health presented the Research Domains of Criteria (RDOC) framework designed to advance etiological research by cutting across diagnostic categories and targeting core dysfunctions. By doing so, it may be possible to focus research on the common etiological mechanisms which lead to specific mental dysfunction. Although the DSM-5 and RDOC now exist, currently available evidence is mostly based on the DSM-IV-TR and prior versions.

In summary, the etiological picture developed using the reliable system of DSM classification has limits. Existing challenges are readily apparent in the study of late-life depression. Sub-diagnostic depressive syndromes are very common among older adults, but it is unclear whether these represent a separate or simply less severe version of the same phenotype; uncertainty follows regarding which causal pathways to target in preventative interventions. Thus, research examining the range of related symptoms, within and across disorders, is needed to refine our description of common late-life depressive phenotypes (regardless of diagnostic criteria) as well as their causal origins.

1.1.3 Measurement of Depression in Aging Research

Diagnostic instruments: In large-scale research, clinical judgment is rarely employed for the purposes of diagnosis because it is usually unreliable or cost-prohibitive. Two main fully-structured instruments are used instead to operationalize DSM nomenclature in research: the Diagnostic Interview Schedule (DIS) [21] and the Composite International Diagnostic Interview (CIDI) [22]. The Structured Clinical Interview for DSM (SCID), a semi-structured instrument, is

also available but can only be administered by individuals with clinical training [23]. These instruments are considered gold-standards in psychiatric epidemiologic research, and continue to be updated in step with revisions to official nomenclature. Test re-test reliability has been demonstrated to be higher in both the DIS and CIDI compared to semi-structured clinician interviews [24].

Fully-structured and computerized, the DIS and CIDI can be administered by lay-people to render a diagnosis of past month, past year, or lifetime mental health disorders. One study showed that the CIDI was a valid diagnostic instrument for research in a medically ill population [25]. The DIS was demonstrated to have similar sensitivity and specificity (compared to a clinical diagnosis) between medically ill older and younger adults [26]. Although limited research has compared the performance of these structured instruments by age, a recent study raises questions regarding the validity of these structured instruments for use in older adults [27] (discussed in Section 1.1.2).

Symptom Scales: Depending on the purpose and aims of a study, the overall cost of administering structured diagnostic instruments may exceed the added value. This is especially true when there is an interest in overall mental well-being, requiring multiple aspects of mental health to be assessed. Indeed, researchers may be interested in symptom patterns rather than clinical diagnoses. Many instruments are available to measure depressive symptomology in general population-based or community research, and these symptom scales have also been developed for screening purposes.

The Montgomery-Åsberg Depression Rating Scale (MADRS) was developed specifically to detect changes within individuals over time. One report provides evidence that the MADRS is more sensitive to change than the Beck Depression Inventory (BDI) [28], although another study

found no difference [29]. The sensitivity of other scale's to change has been examined less often. Although most scales have been developed to be used for screening purposes in the general population, the Geriatric Depression Scale (GDS) [30] was developed specifically for older adults.

The criterion validity of many instruments (compared with an MDD diagnosis) has been examined in community, clinic, and nursing home settings (Table 2). Because most validation studies were conducted in separate samples and often using different threshold values, direct comparisons of sensitivity/specificity are unwarranted. Generally these studies have shown better sensitivity than specificity. These scales can be said to measure the level of depressive symptomology, however they do not systematically determine several key diagnostic requirements, namely: illness duration, whether the episode occurs secondary to another cause (i.e. physical illness), and whether the symptomology is associated with significant functional impairment.

A limited evidence base directly compares the performance of these screens. In a study of older primary care patients [31] using SCID-determined MDD as the "gold-standard," the Center for Epidemiological Studies Depression Scale – 20 (CES-D 20) and both GDS versions demonstrated similar, acceptable sensitivity and specificity (CES-D 20: 92% sensitivity, 87% specificity; GDS-30: 100% sensitivity, 84% specificity; GDS-15: 92% sensitivity, 81% specificity). This study found that the GDS was associated with minor depressive disorder while the CES-D was not, although both scales lost considerable accuracy screening for less than major depression. As these authors point out, the GDS's "yes/no" response format may add to ease-of-use compared to the likert-style CES-D response options.

A recent systematic review of instruments for screening older adults in hospitals concluded that only the GDS scales have been sufficiently validated in this setting [32]. Among older adults recovering from a stroke, the GDS had higher sensitivity while the CES-D had higher specificity (CES-D 20: 56% sensitivity, 91% specificity; GDS-30: 88% sensitivity, 64% specificity) [33]. In patients with Parkinson's disease, a study comparing nine self-report scales to a psychiatric interview demonstrated a range of sensitivity (66-85%) and specificity (60-88%) for detecting MDD [34]; although most other scales also performed acceptably, of the scales examined, the authors concluded that the GDS-30 was the most efficient due to "brevity, favorable psychometric properties, and a lack of copyright protection".

Arguably the most important health condition affecting depression scale performance is cognitive impairment. Many validation studies exclude participants with cognitive impairment. In a nursing home setting, the sensitivity/specific of the GDS-30 was 63/83%, however when excluding participants with cognitive impairment sensitivity/specificity was 84/91%.

The Cornell Scale for Depression in Dementia (CSDD) was purposely designed to preserve screening validity in older adults with cognitive impairment [35]. In one study the CSDD outperformed the GDS-30 and GDS-15 compared with clinician diagnosis in both demented and non-demented participants [36]. The specificity of the GDS-30 was shown to be low (38%) among patients with dementia, although in the same participants the GDS-15 yielded adequate specificity (85%) [37]. Another study showed that the GDS-15 did not retain validity in the presence of cognitive impairment [38]. However, in patients with mild cognitive impairment (MCI) the GDS-30 performed adequately compared to the CSDD [39], and among patients without dementia the MADRS has been shown to be preferable [40].

The GDS-30 may not be a reliable screening tool compared to the CSDD in the presence of Alzheimer's disease (AD) [39]. In patients with AD, the BDI yielded low sensitivity and moderate specificity [41]. The CSDD, however, requires a proxy informant which is not always feasible and performance comparisons may therefore one-sidedly reflect methodological (as opposed to questionnaire) driven differences. Dementias may affect scale sensitivity by causing symptom under-reporting, while scale specificity can also be negatively impacted since cognitive impairment mimics mood disturbance; the ontogeny of late-life depression may differ in the presence of cognitive impairment. Proxy informants may be required to assess the burden and course of mood disturbances when occurring alongside cognitive impairment. Future research is needed to both clarify and optimize the validity of screening instruments in patients with cognitive impairment.

In addition, other factors may affect the performance of these screens. Papassotiropoulos and colleagues [42] showed that false positives using the CES-D were more common for participants living in an old age residence or with family members (compared to those living with a spouse). Mottram et al. [43] demonstrated that sensitivity/specificity of both the MADRS and HAM-D was acceptably invariant across gender and age groups. Another study found that CES-D 20 false positives were no more likely among participants with physical illness, cognitive decline, or anxiety symptoms [44].

Despite finding a range of sensitivity/specificity within and across instruments, current evidence demonstrates that it is possible to screen for MDD among cognitively intact older adults with a high degree of sensitivity. Further research is needed to assess the validity of measurement in the presence of factors, like cognitive impairment, which may bias participant responses and threaten overall interpretability. Questionnaire development should target scale

specificity in order to provide clinical context when assessing depression symptoms in epidemiologic studies of older adults. Adding simple questions may improve scale validity, for example, assessing the duration and the severity of emotionally attributable functional impairment. Instruments measuring common depression symptoms are important tools which make assessing the burden and etiology of mood feasible in a wide variety of research settings.

1.2 DESCRIPTIVE EPIDEMIOLOGY

1.2.1 Prevalence of depression and aging

Using a data-driven approach applied to nationally representative data (the Epidemiological Catchment Area (ECA) Study), Mezuk & Kendler [45] identified four-classes of participants: (1) non-depressed (83.2%), (2) those with mild depression (11.6%), (3) severe depression (1.9%), as well as a (4) despondent (3.2%) group. Among the despondent group, the probability of endorsing most symptoms was intermediate between the mild and severe depression group, with a few exceptions: the despondent and severe groups had similar probabilities of endorsing suicide items; however, compared with mild and severe depression groups, despondent participants had a lower probability of neurovegetative symptoms.

The authors reported the prevalence of LCA derived sub-groups by age groups. It is important to note that adults 65+ in the ECA study were born during or before 1920, and the latent structure of depression may differ among more recent cohorts of older adults. Findings show the prevalence of the severe depression sub-group was inversely associated with age; prevalence estimates within each age group were: 2.3% for 18-29 year olds; 2.0% for 30-44 year

olds; 2.0% for 45-64 year olds; and 1.3% for ≥65 year olds. The mild depression sub-group (which may or may not meet diagnostic criteria for MDD) followed something like an upside-down "U-shape" with age; the prevalence for this sub-group per age group were 6.9% for 18-29 year olds; 12.2% for 30-44 year olds; 11.7% for 45-64 year olds; and 9.7% for ≥65 years old.

The prevalence of the despondent group by age appeared to follow a "J-shaped" curve (18-29 years: 7.5%; 30-44 years: 1.8%; 45-64 years: 1.1%; ≥65 years: 2.0%). Among the group of adults who were ≥65 years old, the despondent class was more prevalent than the severely depressed class. These authors note that longitudinal research is needed to directly examine transitions across latent states over time. Finding differences in patterns of sub-type expression across the life course begs the question of whether survival bias might lead to highly selected samples of older adults. Indeed, participants aged ≥65 in this study were 60.1% women indicating that survival did affect sampling.

Nationally representative samples have consistently found a lower prevalence of MDD among older adults (Table 3). One major limitation is that nationally representative samples have reported on older adults as a single age group (65+). Characterizing all adults 65+ as a single group may hinder our understanding of the life course of depression, as the prevalence of depression may vary by age post-65 years (i.e. comparing adults 65-69 vs. 70-74; see discussion of age effects below).

Prominent late-life depression researchers Drs. Celia Hybels and Dan Blazer noted in a review paper (citing their own prior review) that "most epidemiologists agree the contribution of methodological and sampling bias…is small" [46]. Before discussing the possibility of true age and cohort effects, we first consider how selection and measurement bias may result in perceived differences in MDD prevalence across the lifespan. Dr. Blazer suggests that the accumulated

evidence regarding selection bias and differential symptom endorsement is not substantial (Personal Communication, 11/14/2013). However in addition to differential symptom endorsement within scales by age, evidence suggests that variation in measurement methodology can lead to substantial differences in prevalence estimates for older adults [27, 47] .

With regard to selection bias, Dr. Blazer stated that only about 4% of older adults live in institutional settings and that this proportion is decreasing. Nevertheless, if the prevalence of MDD among elders living in institutional settings is very high, this will lead to a non-trivial increase (for example, 25% with MDD among 4% institutionalized older adults could lead to a 1% increase in the overall prevalence estimate). Finally, Dr. Blazer also expressed that "we do not believe that survival bias is a factor except with the more severe depression," however recent evidence suggests that the depression-survival association is not restricted to severe cases [6]. We briefly review these potential explanations for observed differences in MDD prevalence across the lifespan.

Selection Bias: Differential survival may lead to sampling bias. Indeed, in a meta-analysis of 25 community-based studies the pooled relative risk of dying in depressed subjects was 1.81 times that of non-depressed participants [48]. A more recent study in a nationally representative sample found that the elevated mortality risk associated with depressive symptoms was accounted for by physical health problems [6]. Regardless of whether MDD contributes to mortality independent of other known risk factors, if people with or prone to depression are characteristically more sick and likely to die earlier, they are less proportionally likely to survive to be included in study samples.

Another source of selection bias pertains to planned or *de facto* exclusion of medically ill/institutionalized individuals. The NESARC and NCS-R did not include adults living in an

institutional setting. In addition, compared to younger age-groups, on average, older adults suffer from a higher burden of disease and disability and may be thus disproportionately predisposed towards non-participation. The same older adults who are sicker and potentially less likely to participant in studies are more likely to have MDD.

The prevalence of MDD increases from the community to primary care settings, and prevalence further rises in an inpatient setting [49]. *Current* depression is prevalent among 6.5% of older adults in primary care [50], exceeding the average prevalence of current or past year MDD for all age groups in national studies included in Table 3 [9, 51, 52]. In hospitals, the prevalence of MDD among older adults was found to be 11.5% in one study [53], and ranging (depending on the hospital) from 14.2 to a startling 44.5% in another study [54]. In nursing homes, which again are not typically included in epidemiological samples, the prevalence of MDD among older adults is consistently three-four times higher than in a community setting (8.1-12.4% [55, 56]). Therefore, the older adults most susceptible to MDD may also be the least likely to participate in community-based studies.

Measurement Bias: Older adults may fail to recall earlier depressive episodes, thereby lowering lifetime prevalence estimates. Another explanation for differences in prevalence rates by age may be that depression is expressed differently across the lifespan. If this were the case, depression might be equally prevalent in older adults, however it may not be captured using standard criteria and instruments. Particular depression symptoms are in fact reported more or less often depending on age. In the ECA study, the prevalence of almost every depression symptom significantly differed across age groups. For example, 12.0% of adults ≥65 years of age reported insomnia symptoms while 9.6% of the youngest adults reported these symptoms; 5.2%

of the youngest adults reported hypersomnia compared to 1.6% of older adults [57]. Older adults with MDD tend to have fewer crying spells than younger depressed adults [58].

Patients with late-onset depression may be more likely to have weight loss and gastrointestinal symptoms than early onset patients [59], and regardless of disease onset, differences in symptom expression are found when comparing adults <44 to adults >65 [60]. Older patients are less likely to report sadness, a cardinal symptom of diagnosable MDD (>60 vs.18-59[58, 61], >65 vs. <65 [61]). Somatic symptoms which are common in older adults may not attributed to physical rather than mental disease; one small study showed that respondents 55-75 years old were more likely than respondents aged 25-40 to attribute their symptoms to a physical illness, thus excluding them from meeting MDD criteria [62]. However, a re-analysis of the ECA study which allowed symptoms with physical attributions to be counted as psychiatric symptoms demonstrated that subsequent prevalence increases were consistent across all age groups [63]; that is, removing the physical attribution exclusion for symptoms did not result in a disproportionate increase in prevalence among older adults. Because this single study was conducted using data from the ECA study in which older adults (>65) were born before 1920, future studies are needed among more recent cohorts to determine the extent to which older adults would qualify for MDD if it were not for the physical illness exclusion.

In addition to differences in symptom expression and physical attributions, differential measurement error may bias prevalence estimates. In the CIDI, participants must endorse a screening item to enter the depression module, either: “In the past 12 months, have you had two weeks or longer when nearly every day you felt sad, empty, or depressed for most of the day?” or “In the last 12 months, have you had two weeks or longer when you lost interested in most things like work, hobbies and other things you usually enjoyed?” As pointed out by Karlsson et al. [64],

semi-structured interviews allow for more liberal diagnostic decision making than the structured instruments which find that MDD prevalence is lower among older adults. These authors demonstrated that altering the criterion of “depressed mood all of the day” to “depressed mood most of the day” or “depressed mood half of the day” changed prevalence estimates from 4.67 to 9.23 and 11.29%, respectively.

O’Connor & Parslow examined this potential source of age-related measurement bias by assessing concordance in reporting depression between the CIDI and a more simple measure of mood disturbance [27]. While the prevalence of CIDI-based MDD fell sharply with aging, simpler questions probing mood disturbance were mostly age-invariant. Importantly, the level of inconsistency between simple and complex questions about depression rose within subjects sharply beginning at ages 55-64. These authors conclude that older adults may have difficulty processing complex questions and default to non-endorsement. This finding suggests that the measurement error may substantially and differentially influence prevalence estimates by age.

Age Effects: In the Longitudinal Aging Study Amsterdam, the prevalence of MD increased from 1.3% among adults ages 55-59, to 2.7% among adults 80-85 [65]. In the Cardiovascular Health Study, the prevalence of depressive symptoms increased with age among men and women >65 years of age [66]. In the Baltimore Longitudinal Study of Aging, depressive symptoms appeared to peak in young adulthood, decrease across middle adulthood, before increasing again in later life [67]. A recent meta-analysis demonstrated that increasing age is associated with increased risk for mood disturbance across all age groups spanning from 60-85, however the risk of depression did not increase with age after 85 years [68].

The same positive association between age and depressive symptoms was observed in the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE) study.

However, when adjusting for socio-demographic and health factors this pattern reversed so that it appeared that age was inversely associated with depressive symptom levels [69]. It is important to remember that, to the individual and population, the burden of depression is nonetheless real (when it is attributed to disease and disability). Because physical health and other factors that account for the increase in depressive symptoms with age are thought to be modifiable, it is possible that by eliminating or minimizing such causes, many cases can be prevented.

Cohort Effects: Cohort effects potentially explain age-related prevalence trends. Survivors of "hard" times including WWII and the Great Depression may have been healthier across their life, and/or may find living today to be relatively easy [46]. Yang [70] demonstrated that age-related declines in depressive symptom levels were more rapid for earlier cohorts. MDD later in life may be more common among the post-WWII "baby boom" generation; reporting for the NESARC study, Hasin et al. noted that the highest life-time prevalence had shifted from younger adults in earlier studies to middle aged adults by year 2000 [9]. Others have noted that late-life MDD is typically an exacerbation of chronic mood disturbance [65]; because a history of MDD is a strong risk factor for developing new MDD [10], the aging of the post-WWII generation may mark the beginning of a new era where late-life MDD becomes more common. In summary, cohort effects appear robust and important, however other explanations for differences in prevalence rates are also viable. Potential selection biases as well as new information regarding age-differential measurement error indicate that cohort and age effects may not entirely explain the differences in MDD prevalence across the lifespan.

It is critical to keep in mind that, regardless of the prevalence of MDD in later life, the prevalence of clinically significant depressive syndromes among community-dwelling older

adults is quite substantial (8-16% [12]) and may increase with age (see above). In a review of 34 studies, Beekman et al. [71] noted that although MDD was relatively rare (1.8%) in older adults, minor depressive disorder was present in 9.8% of participants; all depressive syndromes combined to an alarming 13.5% prevalence among older adults. In primary care settings, 5.2% of study participants had minor depression and 9.9% had subsyndromal depression [50]. In a nursing home setting, 14.1% of older adults suffered from minor depression with an additional 24% reporting clinically significant sub-clinical depressive symptoms [56]. Depressive syndromes are therefore quite common among older adults.

1.2.2 Incidence of depression and aging

MDD is a chronic disease and prior depressive episodes are a strong risk factor for future occurrences [10]. First onsets of MDD occurring in late-life are therefore may represent a variation from the typical disease phenotype. Late onset MDD is characterized, at least, by a prolonged latency period and possibly different etiological mechanisms. First-onset MDD in late life is relatively rare: the ECA study found that among adults ages 65+ new onset of MDD occurred at a rate of 1.25 per 100 person years [72].

In the Netherlands Mental Health Survey and Incidence Study, no statistically significant differences in the incidence of MDD were found across age groups, although no adults aged 65+ were included [73]. Their data suggested that among men but not women, MDD incidence peaked in younger adult years. In a nursing home setting, MDD incidence was 13.6 per 100 person years [74].

It is generally recognized that among older adults the rate of incident clinically significant depressive syndromes is higher than that of MDD [46]. When including episodes of

clinically significant depressive symptoms, incidence rates more than double among community-dwelling older adults [75]. In a systematic review, Buchtemann et al. [76] found that among older adults, the rate of incident depressive syndromes was 6.8/100 person years. In this review, incidence rates were generally higher in females than males, although associations of age and incidence were found to be inconsistent. In a primary care setting, one study found that the incidence of depressive symptoms was 3.54 per 100 person years for adults 75-79, while among adults 85+ years of age the incidence rate rose to 7.52 per 100 person years [77].

1.3 ANALYTIC EPIDEMIOLOGY

1.3.1 Risk factors for late-life depression

In a meta-analysis of risk factors for depression (disorders and syndromes) identified in community-based studies, the following have been associated with increased risk in multiple studies: female gender (pooled OR 1.4, 95% CI: 1.2-1.8), disability (pooled OR 2.5, 95% CI: 1.6-4.8), new medical illness (pooled OR 2.1, 95% CI: 0.4-10.1), poor health status (pooled OR 1.8, 95% CI: 0.5-12.8), prior depression (pooled OR 1.8, 95% CI: 1.1-7.1), recent bereavement (pooled OR 3.3, 95% CI: 1.7-4.9), and sleep disturbance (pooled OR 2.6, 95% CI: 1.9-3.7), [78]. In a primary care setting, risk factors include: mobility, vision, cognitive and memory impairment, as well as smoking [77]. In a nursing home setting, dementia has also been associated with increased risk, while using a hearing aid has been associated with relative resilience [74]. Perhaps the most broadly relevant factors are disability, disease (including cognitive impairment), and sleep disturbances.

The relationship between disability and depression is intuitive. Disability can lead to role changes thus serving as a significant stressor, although individual responses to new functional limitations range widely. Although depression is appropriately conceived of as a cause of disability and disease [1, 79], in fact disability is a main contributor to late-life depression [80]. One study demonstrated that over time, an increasing burden of disability was associated with increasing levels of depressive symptoms [81]; change in depression were also positively associated with change in disability, however less strongly so. In another study, disability was robustly associated with new onset depression, while the persistence of depression was predicted by social support rather than disablement [82].

Social support is also thought to be an important factor in depression etiology. Recent research demonstrates that for women, a high need for affiliation was associated with depression risk, while among men different aspects of social support (not having a partner in the household or having a small social network) predicted depression onset [83]. Marriage may be protective for men, but a risk factor for women [82]. Personality factors have also been related to depression, for example environmental mastery, purpose in life and autonomy have been related to depressive symptoms among nursing home residents [84]. Another study showed that social support modifies the relationship of neuroticism and openness with depression [85]. Because most prior research is cross-sectional, future longitudinal research is required to evaluate the roles of personality and social support over time and as potential determinants of depression following incident health/life events. Although depression and personality were examined as predictors of health status in the Veterans Administration Normative Aging Study [86], no community or general population-based research has examined personality as a predictor of *future* depression.

Chronic pain and depression are also likely related. Chronic pain may worsen depression while depression may worsen chronic pain [87]. In the Baltimore ECA study sample, however, depression was associated with increased risk for incident back pain over long periods of time while pain was not related to future depression [88]. Future research is needed to clarify potential bi-directional relations between depression and pain.

Other illnesses contribute to depression risk through a range of potential mechanisms. One of the most common and impactful health factor among older adults is cognitive impairment. There may be substantial etiological overlap between a portion of dementia and depression cases in late life. The "vascular hypothesis" of late-life depression suggests that cerebrovascular changes including white matter hyperintensities [89] cause depression; vascular causes of dementia have been recognized and catalogued for at least two decades [90]. Cognitive decline can certainly serve as a stressor (i.e. disintegrating the social environment) leading to depression. At the same time, in meta-analysis, late-life depression has been associated with increased dementia risk [14]. It is unclear whether depression exerts a causal effect on dementia risk or if a single mechanism causes both depression and dementia.

Another potential source of overlap between illness and depression in older adults involves the inflammatory response. In younger adults, administration of endotoxin raises levels of inflammatory markers and causes a "sickness-like" behavior characterized by low mood, tiredness, and social withdrawal [91, 92]. When treated with interferon-alpha, which also increases levels of inflammatory cytokines, patients are at an increased risk for developing depression [92, 93]. In an elucidating study using time-lagged predictors, levels of interleukin-6 were found to predict subjective sleep disturbances which subsequently predicted levels of

depressive symptoms [93]. However this study examined younger adults in the process of treatment for hepatitis C, and these findings must be replicated in epidemiologic studies of aging.

Five cross-sectional studies, including our own prior work, tested whether raised levels of inflammatory markers are associated depression in older adults [94-98]. Our research suggests that the relationship between inflammatory markers and depressive syndromes in older adults may differ depending on age [98]. In additionally, sleep characteristics may represent a residual confound in previously identified associations of inflammatory markers and depression. In a prospective study, Milaneschi et al. [99] demonstrated an elevated risk for developing clinically significant depressive symptoms in late-life on the basis of interleukins – 1 receptor agonist levels. Future longitudinal work is needed to replicate this finding and examine the role of sleep disturbances in these etiological pathways across the lifespan.

1.3.2 The central role of sleep in late-life depression

Sleep disturbances are a common symptom of depression. About 74% of men with clinically significant depressive symptoms in the MrOS Sleep Study also reported poor subjective sleep quality. Sleep problems in late-life depression can be heterogeneous, although more older adults report insomnia and daytime sleepiness complaints than hypersomnia [57]. Older adults with mood disturbance tend to have difficulty falling asleep, maintaining sleep, and report waking early in the morning without being able to return to rest [100]; insufficient sleep quantities and reports of non-restorative are also common among older adults with depression.

Depression also correlates with altered sleep architecture. In laboratory based studies, depression has been consistently associated with an increased percentage of sleep time spent in rapid-eye movement (REM) sleep (i.e. see [101]). In the first epidemiological investigation of

these relationships among older adults, we found that depressed mood was instead associated with a lesser percentage of time spent in REM sleep [102]. This finding suggests that the relationship between mood and depression may be modified by age, and future research is needed to clarify the nature of these associations across the lifespan. REM sleep deprivation contributes to a reduction in hippocampal neurogenesis in rats [103], and in humans recent data suggests that disrupted slow-wave sleep may be related to prefrontal atrophy and hippocampal-dependent memory [104], altogether suggesting that sleep architecture may reflect a process central relevant to both mood and cognition.

At least since an early report by Ford and Kamerow [13], sleep problems have been recognized to increase depression risk. These authors noted that individuals who reported sleep disturbances were at a significantly increased risk for developing depression. In another study, having 3-4 symptoms of insomnia predicted over 3 times the risk of incident depression [105]; in this study, objectively measured sleep latency, continuity, and duration were all significant predictors of depression. In the French Three-City Study of older adults, difficulty falling asleep, difficulty maintaining sleep, and excessive daytime sleepiness were associated with an increased risk of developing depressive symptoms although early morning awakening was not [106].

The MrOS Sleep Study recently reported that objectively measured sleep disturbances were related to future risk for depression among community-dwelling older adults [107]. While associations between objectively measured sleep characteristics and depression risk were attenuated after adjustments for baseline levels of depressive symptomology, subjectively assessed sleep disturbances remained robustly related to depression risk after multiple covariate adjustments[107].

Mood and sleep disturbance are thought to be bi-directionally related [108]. Our recent systematic review of factors associated with incident sleep disturbances among older adults found that in 10/13 studies reporting, depression was associated with an increased risk of developing sleep disturbances (odds ratios ranged from 1.54 to 9.18 [109, 110]). Of the three negative studies reporting on depression, two had marginal ($p=0.06$) associations with worsening sleep [111, 112], and the other was the only to examine a lifetime (as opposed to current) episode of depression as a predictor [113]; temporal proximity may be an important determinate of these risk relations.

Sleep disturbances may mediate the relationship between physical health problems and mood disturbances. For example pain may lead to sleep problems, subsequently exacerbating mood disturbance. Incident disability, health events, or other stressful events may lead to mood disturbance by altering the daily pattern of rest and activity. Recently, these rhythmic patterns of sleep-wake activity were been examined as a potential correlate [114] and risk factor [115] for depression. Older adults with depressive symptoms tend to exhibit less robust daily patterns of rest and activity. Among community-dwelling older men, less robust rest-activity rhythms were found to independently predict significant increases in depressive symptoms, above and beyond numerous relevant covariates including sleep complaints and self-reported physical activity. Future research is needed to further understand the nature of sleep-wake rhythms and their relation to depression risk. The biological pathways relating sleep, circadian rest-activity rhythms, and depression among older adults are unknown. In addition, the hypothesis that stressful life-events (i.e. bereavement and incident disability) may lead to depression by disrupting sleep-wake rhythms remains currently untested.

1.4 TABLES AND FIGURES

Table 1. DSM-IV-TR Criteria for Major Depressive Disorder (MDD)

-Depressed mood or a loss of interest or pleasure in daily activities for more than two weeks. -Mood represents a change from the person's baseline. -Impaired function: social, occupational, educational. -At least 5 of the 9 symptoms below, present nearly every day:
1. Depressed mood or irritable most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
2. Decreased interest or pleasure in most activities, most of each day
3. Significant weight change (5%) or change in appetite
4. Change in sleep: Insomnia or hypersomnia
5. Change in activity: Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Guilt/worthlessness: Feelings of worthlessness or excessive or inappropriate guilt
8. Concentration: diminished ability to think or concentrate, or more indecisiveness
9. Suicidality: Thoughts of death or suicide, or has suicide plan

Table 2. Sensitivity and specificity of self-report depression screens in older adults compared to a diagnosis of current MDD

Setting:	Community		Primary care/hospital		Nursing home	
Scale (# items)	Cut-point	Sensitivity/ Specificity	Cut-point	Sensitivity/ Specificity	Cut-point	Sensitivity/ Specificity
HAM-D (17)			15/16	87.5/99.1[43]		
CES-D (20)	9/10	75/72[42]	21/22	75/51 [116]		
	15/16	100/87.6[44]	16/17	100/57 [117]**		
			21/22	92/87 [31]		
			19/20	56/91 [33]		
CES-D (10)			3/4	100/92 [118]		
			11/12	76/55 [116]		
			8/9	91/35 [119]		
GDS (30)	11/12	75.3/77[120]*	10/11	85/82 [32]*	10/11	96.3/69.1 [122]
	10/11	73/65[121]	10/11	91/42 [37]	10/11	89/68 [123]
			9/10	92/81 [31]	10/11	69/86 [124]
			9/10	88/64 [33]	10/11	88.89/56.41 [125]
GDS (15)	5/6	80.5/75[120]*	5/6	79/77 [32]*	5/6	96.3/75.7 [122]
			5/6	90.9/64.5 [126]	5/6	95/83 [127]
			5/6	83/69 [37]	5/6	88/65 [123]
			4/5	92/81 [31]		
MADRS (10)			20/21	72.1/98.9 [43]		
				82/75 [128]		
PHQ (9)	4/5	80/78[129]	9/10	80/92 [130]		
PHQ (2)	0/1	100/77[131]	2/3	83/83 [130]		

* Pooled estimate; **orthopedic patients criterion validity shown - neurological patients sensitivity/specificity was 100/36.

Table 3. Lifetime Prevalence of MDD by Age Group in National Studies

First Author	Study	Year conducted	Age groups	Prevalence (%)
Weissman [132]	ECA	1980-1985	18-24	6.7
			25-44	9.5
			45-64	5.0
			65+	2.0
Kessler [133]	NCS-R	2001-2002	18-29	15.4
			30-44	19.8
			45-59	18.8
			60+	10.6
Hasin [9]	NESARC	2000-2001	18-29	12.02
			30-44	14.03
			45-59	14.91
			65+	8.91

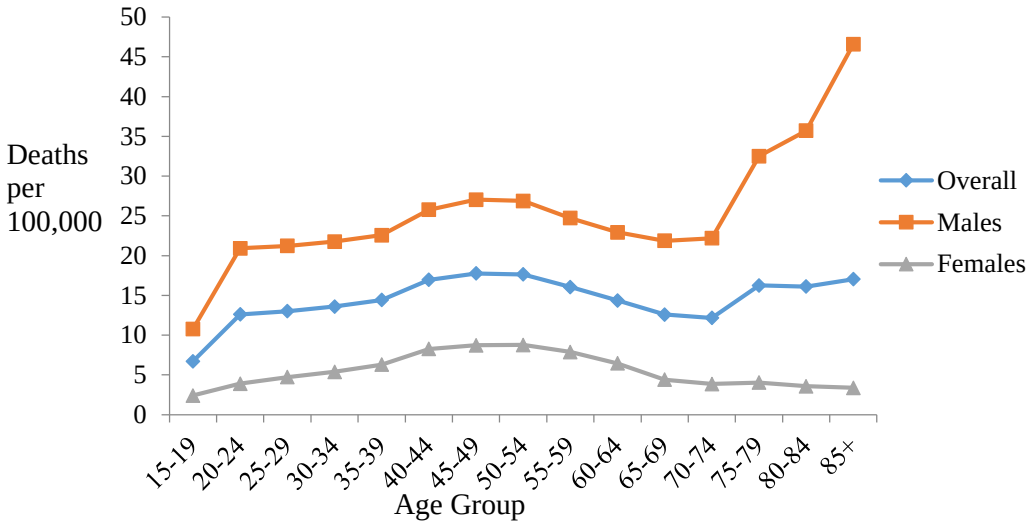

Figure 1. Suicide death rates per 100,000 by age and sex

2.0 LATENT CLASS ANALYSIS OF SLEEP, CIRCADIAN REST-ACTIVITY, AND DEPRESSIVE SYNDROMES AMONG OLDER MEN

In this chapter we use a data-driven approach to assess the commonly occurring sleep, circadian rest-activity rhythm (CAR), and depressive syndromes among older men. Using Latent Class Analysis (LCA) we found that only 53.86% of our sample was free from some type of probable depressive syndrome, while only 45.17% had no sleep disturbances, and 32.18% had all normative CAR parameters. Subjective sleep disturbances were very common, but a dissociation with objectively assessed disturbances was observed such that only a sub-set (8.87%) experienced both, while 37.46% had only subjective and 8.51% had only objective disturbances. Mental health and medication use appeared to correlate with subjective disturbances, whereas physical health correlated with objective disturbances. CAR classes were distinguished by timing, rhythm height, as well as the length of the active period. Physical health and lifestyle factors were among the unique correlates of CAR latent classes. Depressive syndromes characterized by somatic/apathy symptoms were very common, whereas psychological/cognitive symptoms were relatively rare; emotional impairment was common and distinguished the depression classes. Clinical and sub-clinical physical disease were among the unique correlates of membership in the identified classes. Overall, our findings demonstrate substantial heterogeneity and a high prevalence of sub-diagnostic sleep, CAR, and depressive syndromes among older men. Preventing physical health problems may reduce the prevalence of these

syndromes. Future work should attempt to replicate these configurations of signs/symptoms in other samples.

2.1 INTRODUCTION

Despite their high prevalence [12, 134], little is known *sub-diagnostic* late-life sleep and depression syndromes. Especially given that the global population is rapidly aging [8], research is required to assess the clinical significance and long-term consequences of these syndromes. Thus, assumption-free surveillance of late-life sleep and depressive syndromes is a major public health priority.

In other words, several high priority epidemiologic research questions require detailed investigations into the nature, prevalence, and clinical significance of common sign/symptom patterns *without making a priori assumptions about what constitutes meaningful disease*. In depression, for example, questions that cannot be answered relying upon MDD criteria alone include: Are syndromes which do not meet MDD criteria simply a less severe version of the same, single depression phenotype? Do sub-diagnostic syndromes differ in terms of their signs/symptoms, physical health correlates, or biological substrates? Are the long-term consequences of syndromes similar to those of than MDD?

Epidemiology is tasked with answering these questions. Specifically, the core purposes of epidemiology include: defining syndromes, assessing their prevalence, and understanding their causes/consequences [135]. Assessing the potential phenotypic distinctness and consequences of common late-life sub-diagnostic syndromes can inform developmental studies of clinical disease and also provide evidence to base wide-reaching primary and secondary interventions.

Among techniques to examine naturally occurring syndromes *without intrinsic dependence or reference to known/existing categorization schemes* is latent class analysis (LCA). LCA is a data-driven method which identifies sub-groups with similar patterns of signs/symptoms, thus providing a description of the syndromic states found in a sample. Using LCA, one can assess the types of sign/symptom patterns found in a sample, and further, assess their prevalence, correlates, and consequences on distal health outcomes. In the current chapter, we present all but the latter among a large sample of well-characterized community-dwelling older men. In the next chapter we examine the data-derived groups' association with rates of change in overall depressive symptomology over time (Chapter 3).

2.1.1 Rationale for depression LCA

LCA has been previously applied with enthusiasm to study depression. In a nationally representative sample (the National Epidemiologic Survey on Alcohol and Related Conditions) Carragher et al. [45] identified four latent sub-groups characterized by: (1) minimal depressive symptoms (18.8%), (2) psychosomatic symptoms (30.6%), (3) cognitive-emotional symptoms (10.2%), and (4) severe depression (40.9%). This study was limited by the use of screener or "gateway" questions, such that only participants endorsing one of the two core mood disorder questions contributed data on depressive symptoms. Therefore, potential depressive syndromes which do not include either of these symptoms were entirely excluded.

Despite this and other prior work, a systematic review of latent models of depression (n=10 LCA studies not isolated to older adults) concluded that there is insufficient empirical support for depression sub-types beyond severity-based distinctions [19]. Even less research using LCA has been conducted among older adults. Hybels and colleagues applied LCA to study

symptom profiles of older adults with MDD using the CES-D and HAM-D [136]. Note that application of the MDD inclusion criteria ensures, like studies with gateway questions, syndromes lacking core features of MDD (the known disease entity characterized by low mood and anhedonia) are excluded from studied. Four sub-groups of MDD patients were identified based on the CES-D scale.

These classes varied consistently as a function of symptom severity: one cluster had the mildest symptoms (8%), another had generally moderate symptoms (but lacked interpersonal symptoms; 36%), and a third generally had less severe symptoms than the moderate group (with similar amounts of the psycho- somatic/motor symptoms of restless sleep and reduced talking; 34%). The final cluster consisted of participants with the most severe symptoms (22%). For the HAM-D, a three cluster solution was best, however these clusters appeared to vary as a function of symptom severity. Another LCA from this research group in a general sample of community-dwelling older adults used the MADRS but again found symptom profiles differing mostly in terms of severity [137].

A report from the Cache County Memory Study of older adults identified 3 sub-groups differing in terms of overall severity and symptom expression [138]; however this study only included participants who endorsed “gateway” questions (n included = 400 out of a total 5092 participants). The latent classes identified were: (1) symptom levels consonant with major depression (61.5%), (2) moderate symptom levels that could indicate either major or minor depression without loss of interest in activities (17%), and (3) milder symptomology resembling minor depression (21.5%). The moderate and mild symptom groups were distinguished by: a complete lack of “loss of interest” in the moderate group, and a lower level of sleep problems and neurovegetative symptoms in the mild group.

To my knowledge, no prior study has examined the nature, correlates, and consequences of data-derived late-life depressive syndromes in a large unselected of community-dwelling older adults (not requiring a diagnosis or "gateway questions" as inclusion criteria). It is worth highlighting that Hybels et al. [137] previously performed a latent-class analysis of depressive symptoms in an unselected sample; these researchers then examined how latent sub-group membership was related to future change in depressive symptoms over time. This work provides an excellent substantive and methodological precedent, however it did not include a detailed examination of the health correlates of being in the identified latent depression subgroups

2.1.2 Rationale for sleep LCA

No known prior study has used LCA to assess/describe within-person patterns of specific subjective and objective sleep disturbances. We aim to examine the RDOC sleep/arousal domain on both self-report and behavioral (actigraph) levels. Subjective sleep reports are easily obtainable and are the only source of information regarding perceived sleep quality. However, perceived sleep characteristics may not completely concord with objective sleep measures like sleep duration or the level of fragmentation. LCA can determine which particular subjective/objective sleep disturbances tend to co-occur and how common any distinct disturbance patterns are.

An additional reason to apply LCA to comprehensively characterized sleep is to assess the precise nature of long recognized sleep-associated depression risk [13]. Among older adults, and indeed, generally, little evidence exists isolating the specific aspects of sleep related to depression risk. Recent research among older men suggests that subjective, but not objective disturbances are related to future depression [107]. LCA can cut through between-person

heterogeneity to determine how various sleep problems commonly co-occur, and this improved sleep phenotype categorization can be used in future investigations of depression risk (Chapter 3).

2.1.3 Rationale for CAR LCA

Rest and activity exhibit diurnal variation known as the CAR. Recent research demonstrates that specific characteristics of the CAR are relevant to a wide range of health outcomes in aging. Aspects of the CAR have been associated with future depression [115], cognitive impairment [139], cardiovascular disease [140], and mortality [141]. These studies provide important examinations of specific aspects, such as the height, robustness, or timing, of the CAR in relation to future disease.

In reality, however, each person has parameters for all aspects of the CAR. The within-person configurations of CAR parameters commonly found in the community are unknown. For example, do dampened activity patterns often co-occur with phase delays or advanced? Application of LCA to study CAR disturbances can determine which patterns of CAR disturbances are observed and how often.

In addition, focusing on each aspect separately may neglect interactions wherein specific combinations of parameters synergistically influence health. Given multiple CAR parameters including rhythm height, timing, and robustness, traditional testing of interactions based on *a priori* hypotheses can become cumbersome. LCA provides a manageable method for understanding which patterns of CAR disturbances are found in a sample (thus which are important research targets) and whether/which configurations are related to distal health outcomes.

2.1.4 Cross-sectional Aims

Given the above-mentioned rationale, we applied LCA to sleep, CAR, and depression domains to accomplish the following specific aims:

Aim 1: Understand the specific patterns (combinations) of signs/symptoms occurring within three separate domains (sleep, CAR, and depression) among older men.

Hypothesis 1(a): Heterogeneity in the overall severity of sign/symptom patterns will be observed within each (of three) domains.

Hypothesis 1(b): Substantial sub-samples within each domain will have mild syndromes:

In the sleep domain, subjective sleep complaints will be common.

In the CAR domain, having reduced locomotor activity alone will be common.

In the depression domain, mild apathy/somatic symptoms will be common.

Hypothesis 1(c): Within each domain, at least one smaller portion of the sample will have additional serious complaints:

In the sleep domain, a subset of the sample experiencing subjectively poor sleep will also have objective measures of insomnia (prolonged sleep onset latency, sleep fragmentation, and short sleep). Prolonged sleep onset latency will also co-occur with long sleep duration and daytime sleepiness.

In the CAR domain, a portion of those with overall reductions in locomotor activity will also have a dampened rhythm and/or an erratic rest-activity pattern. Late-timing will often co-occur with this more severe CAR syndrome.

In the depression domain, a portion of those with somatic symptoms will also report psychological symptoms and signs of impairment.

Aim 2: Determine the unique physical and mental health correlates of specific sleep, CAR, and depression syndromes found in the community.

Hypothesis 2(a): Anxiety, less physical activity, worse cardiovascular health, and instrumental activity of daily living (IADL) impairment will be associated with commonly occurring mild syndromes within each domain.

Hypothesis 2(b): The correlates of mild syndromes within each domain will be similar, whereas across domains, the correlates of more severe syndromes will be nuanced.

2.2 METHODS

2.2.1 Participants

The Osteoporotic Fractures in Men (MrOS) Sleep Study was conducted between December 2003 and March 2005 and included 3,135 participants recruited at six clinical centers in the United States (Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Monongahela Valley, Pennsylvania; Portland, Oregon; and San Diego, California) [142, 143]. The parent MrOS study included community-dwelling men ≥65 years who could walk without assistance and were without bilateral hip replacements. Men were excluded from the Sleep Study if they regularly used overnight nocturnal oxygen therapy, positive pressure or oral appliances for treatment of sleep apnea (n=150). Other reasons for non-participation were: death (n=349), terminated study participation (n=39), declined sleep study (n=1997), or because MrOS Sleep Study recruitment goals had already been met (n=324).

Compared with men participating only in the parent MrOS study, the Sleep Study sample tended to be healthier (i.e. percent with past myocardial infarction in Sleep Study=12.44% vs. excluded=15.53%, p=0.0006), more educated, and younger; no differences in race by Sleep Study participation was detected. All men provided written informed consent, and the study was approved by the Institutional Review Board at each clinic site. Participants were included in the analytic cohort if they had ≥3, 24 hour periods of technically adequate actigraph data (excluded n=134). The cross-sectional analysis was therefore initially conducted with 3001 men.

2.2.2 Measures

2.2.2.1 Sleep LCA indicators

Both subjective and objective measures of sleep were considered. Participants were asked to rate their past month overall sleep quality, and response were coded as "very bad"/"fairly bad" versus "fairly good"/"very good." Participants were also asked "during the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?"; response were coded as "not during the past month"/"less than once a week" versus "once or twice a week"/"three or more times a week." From the GDAS participants answered whether: (1) they had been sleeping poorly, (2) they had been waking early, or if (3) they had difficulty falling asleep.

Objective estimates of sleep/wake activity were obtained using the Octagonal Sleep Watch actigraphy, or SleepWatch-O, (Ambulatory Monitoring, Inc, Ardsley, NY). Participants were asked to wear actigraphs on the non-dominant wrist for a minimum of 5 consecutive 24-hour periods except when bathing or during water sports; participants were also asked to keep a sleep log which was used to edit the actigraphy data. Movement was measured using a

piezoelectric biomorph-ceramic cantilevered beam, which generates a voltage each time the actigraph is moved. These voltages are gathered continuously and stored in one minute epochs. Data collected in digital integration mode were used for this analysis. ActionW-2 software (Ambulatory Monitoring, Inc., Ardsley, NY) was used to score the actigraphy data (for scoring algorithms details see [144, 145]). This method produces reliable estimate of sleep-wake patterns [146, 147], and has been shown to have good concordance with total sleep time (TST) from polysomnography [148]. Inter-scorer reliability has been previously found to be high in sleep studies performed by the MrOS Sleep Study team (intra-class coefficient=0.95) [144].

Actigraphy derived sleep parameters used in the sleep LCA were: total sleep time (TST; hours per night spent sleeping in bed after "lights off"), sleep latency (SL; amount of time until onset of sleep defined when participant achieved sleep for 20 continuous minutes after getting into bed) and wake after sleep onset (WASO; minutes scored awake during the interval after sleep onset). Actigraphy measured sleep parameters were dichotomized with the following cut-offs: (1) short sleep <5 and long sleep >8 hours (contrasted in a single variable with 5-8 hour sleepers); (3) SL≥60 minutes, and (4) WASO≥90 minutes.

2.2.2.2 CAR LCA indicators

Actigraph identified bedtime, wake-time, mid-sleep time, acrophase [149] and sleep period [150, 151] generally correlate with that of urinary 6-sulphatoxymelatonin secretion. Diurnal rest and activity variation (the CAR) therefore reflects the central biological pacemaker located in the suprachiasmatic nucleus; because voluntary behavior can "mask" endogenous signal reflected in rest-activity patterns, the CAR may only indirectly reflect circadian biology [146].

A five-parameter extended sigmoidally transformed cosine model with an antilogistic function was used to model activity data; this model fits CAR data better than a standard cosine curve as humans typically exhibits a more “squared” daytime activity rhythm [152]. Modeled parameters included measures of rhythm height, timing, and robustness. For all CAR parameters except timing variables, the lowest quartile was compared with the others to represent deviations the sample’s normative values thus indicating CAR disturbances. For timing parameters, the lowest and the highest quartiles were both compared with the others (in a single variable) to represent both phase advances and delays. Using quartiles to represent non-normative or disturbed CAR parameters is consistent with prior work [115, 139, 141, 153] and, in the context of LCA, is designed to identify sub-groups with specific patterns of CAR parameters outside the normative range (disturbances).

Rhythm height parameters were: amplitude (peak-nadir difference) and mesor (estimated middle of the fitted curve). To assess whether rhythm height reductions were consequences of activity levels overall, rather than relative peak-nadir differences, standardized amplitude was computed as amplitude divided by mesor. Lower values of standardized amplitude reflect a dampened rhythm.

Rhythm timing measures were: acrophase (time of day of peak activity level), up-mesor (time of day when activity passes up through mesor, also known as left-half detection point approximating the time the participant “gets going” in the morning), down-mesor (time of day when activity passes down through mesor, also known as right-half detection point, approximating the time of day the participant “settles down” for the night).

The extended cosine model also provides a measure known as the pseudo-F statistic which reflects of how well the modeled rhythm fits the observed data [152]. Values indicate how

robustly patterned rest-activity is over the assessment period, with lower values indicating poorer model fit and suggesting an erratic and/or variable rhythm.

Finally, a parameter called alpha reflects the relative width of the activity peak compared with nadir; higher values indicate a relative narrowness of the active compared with rest period, thus the highest quartile was contrasted with the others to reflect a shortened activity period.

2.2.2.3 Depression LCA indicators

The Goldberg Depression and Anxiety Scale [154] (GDAS) contains 9 depression and 9 anxiety oriented items. Responses were binary indicators of whether the symptom was "recently" present or absent. The Geriatric Depression Scale-15 [155] (GDS) contains 15 items with binary response options indicating whether the symptom was present or absent over the "last week." Three additional depression items were derived from the Short Form-12 [156]. Two of these captured impairment attributable to emotional issues leading to: (1) accomplishing "less than you would like" or (2) not doing "work or other activities as carefully as usual." The final item was regarding the past 4 weeks, and asked "Have you felt downhearted and blue?" For consistency with the other depression items which had binary response options, responses to questions from the Short Form-12 were dichotomized (as "all of the time"/"most of the time"/"a good bit of the time" verses "some of the time"/"a little of the time"/"none of the time")

2.2.2.4 Covariates

Demographics and lifestyle factors: Age, study site, race, weekly alcohol use, daily caffeine intake, educational attainment, smoking status, and BMI were examined as potential cross-sectional correlates of latent class group membership. The Physical Activity Scale for the

Elderly (PASE; a validated self-report measure of physical activity [157, 158]) was expressed continuously.

Other mental health factors: Cognitive function was measured using the 3MS [159] which was expressed as continuous variable. Anxiety symptoms were measured using the anxiety portion of the GDAS [154] as a continuous score reflecting symptom counts (range: 0-9). In addition, associations of the GDS with LCA-derived sleep and CAR latent classes were examined.

Subjective sleep: The Pittsburgh Sleep Quality Index (PSQI) [160] (range 0-21) was expressed continuously to reflect global sleep quality. The Epworth Sleepiness Scale (ESS) was also expressed as a continuous measure of excessive daytime sleepiness ranging from 0-24. Associations of these factors with sleep latent class were not examined (subjective sleep was a part of the LCA group outcome variable).

Actigraph-derived Circadian Rest-Activity Rhythm (CAR) measures: We examined the above mentioned CAR parameters as correlates of only depression latent classes only. Relationships between actigraph sleep and CAR parameters were not examined because they are derived from the same raw data.

Polysomnography (PSG) assessed sleep disordered breathing (SDB): In-home sleep studies using one night of unattended PSG (Safiro, Compumedics, Inc., Melbourne, Australia) were performed with recording of central electroencephalography, bilateral electrooculography, chin electromyography, ECG, nasal pressure and thermistry (for airflow measurement), chest and thoracic inductance plethysmography, finger pulse oximetry, body position, and leg movements, as described previously [161]. Centrally trained and certified staff members performed home visits for setup of the sleep study units. Using approaches similar to those in the Sleep Health

Heart Study [162], after sensors were placed and calibrated, signal quality and impedance were checked, and sensors were repositioned as needed to improve signal quality, replacing electrodes if impedances were greater than 5000 ohms. Polysomnography data quality was generally excellent, with a failure rate of less than 4% and more than 70% of studies graded as being of excellent or outstanding quality. The apnea hypopnea index (AHI) was computed as the average number of apneas and hypopneas per hour of recorded sleep. Apneas were defined as a complete or almost complete cessation of airflow for more than 10 seconds. Hypopneas were defined as a >30% reduction in amplitude of either respiratory effort or airflow for more than 10 seconds associated with a ≥3% oxygen desaturation [163]. Rescoring studies over time indicates that inter- and intra- scorer reliability (ICC) for the AHI was high (ICC>0.95). The AHI was dichotomized at ≥30 to reflect severe sleep disordered breathing.

Instrumental Activity of Daily Living (IADL) impairment: The number of 5 IADL impairments was expressed as a continuous variable; the five IADLs were: heavy housework, preparing own meals, shopping for groceries or clothing, walking 2-3 blocks, and climbing ten stairs [164, 165].

Chronic disease: Participants were asked if they had a fall in the past 12 months. They also reported whether they had ever received a physician diagnosis of: peripheral vascular disease, osteoarthritis (OA), rheumatoid arthritis, hypertension, stroke, angina, congestive heart failure (CHF), myocardial infarction, diabetes, chronic obstructive pulmonary disease (COPD), Parkinson's disease, renal disease, cataracts, or liver disease.

Inflammatory markers: Serum was collected during morning clinic visits after an overnight fast. A natural log transformation was applied to normalize their distributions which were initially skewed. CRP was measured using the ELISA assay kit from ALPCO (CRP

sensitive ELISA). This assay utilizes a sandwich Enzyme Immuno Assay, in which plate wells are coated with polyclonal antibodies to CRP. The inter-assay CVs ranged from 11.6-13.8%. IL-6, TNF-α, and IFN-γ were assayed using the Human ProInflammatory I 4-Plex Ultra-Sensitive Kit by MSD (catalog #K15009C-4). The sensitivities of the assay were: 0.22 pg/mL for IL-6, 0.49 pg/mL for TNF-α, and 0.40 pg/mL for IFN-γ. Inter-assay CVs range from: 2.0- 9.9% for IL-6, 2.1-6.0% for TNF-α, and 1.8-4.5% for IFN-γ. TNF-αsRII was measured with an ELISA from R&D Systems (Minneapolis, MN; catalog #DRT200). The normal range for TNF-sRII in serum is 1003 – 3170 pg/mL. TNF-αsRII inter-assay CVs range from 3.5-5.1%.

Medications: Participants were asked to bring all medications used within the last 30 days to the sleep examination. Medications were entered into an electronic database and matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA)[166]. Psychoactive medications (antidepressants, benzodiazepines, and non-benzodiazepine non-barbiturate sedatives/hypnotics) were considered based on expected clinical relationships between these drugs and the primary predictors and outcomes. Other medications considered were NSAIDs and corticosteroids due to their relations with inflammatory markers and potentially the outcomes.

2.2.3 Statistical methods

LCA postulates the presence of an unmeasured categorical latent variable that directly causes an observed pattern of indicators (single variable items) within a given set. LCA assumes local independence, in other words conditional independence of the indicators given latent class assignment. All indicators were dichotomous, except in the sleep and CAR domains,

duration/timing variables had three categories (i.e. short sleep vs. normative sleep vs. long sleep duration).

The number of latent groups is selected based on both interpretability and model fit statistics. We used the Bayesian Information Criterion (BIC) to compare models with a different number of latent classes. While a smaller value is favored, BIC may indicate improvements in model fit when adding latent classes that do not reflect additional, distinct, or clinically relevant entities. Therefore, BIC was used to select the optimal number of latent classes, however the number of latent groups was only increased when doing so captured an additional, distinct, and clinically relevant entity. An add-in SAS procedure (PROC LCA) was utilized to conduct the LCA [167]. Solutions with small latent classes (<5% of the sample) were rejected except when the addition of the small group captured expected clinical syndromes (i.e. <5% of older adults are expected to have current depression symptoms consistent with MDD).

Because a large number of depression items were available, we employed a systematic method for indicator selection. The goal was to combine depression items to create a fully descriptive, parsimonious LCA model that was statistically sound and computationally feasible (because we could not include all indicators). Depression indicators were eliminated if they (1) did not possess standalone, certain clinical relevance (i.e. by appearing in the Diagnostic and Statistical Manual of Mental Disorders – 5 (DSM-5) [168] depression sections) and (2) were not influential in separating latent groups. LCA solutions from restricted and inclusive indicator sets were compared to determine if the variables exclusion substantively altered the model. The variables included in each analysis are listed in Table 14.

The first analysis was conducted using only GDS items, then in a second model set, GDS indicators were eliminated as described above. Items which were removed included life

satisfaction, boredom, optimism, anxiety symptoms. These items may generally reflect the severity of true depression and therefore entail, at least, contextual clinical relevance; but by themselves, these items did not substantively impact the model/sub-groups found in the sample.

In an initial analysis of the GDAS, only depression items were selected except "…been waking early" which was excluded and considered in the sleep LCA. In addition, following previous literature suggesting irritability may be an important symptom of depression [169], the "…been irritable" item from the GDAS anxiety sub-scale was considered in the depression LCA. Two items were found in both the GDS and GDAS and were thus redundant; these items assessed (1) hopelessness and (2) loss of energy. The GDS hopelessness item asked "do you feel that *your situation* is hopeless" (italics added) whereas the GDAS item offered improved interpretability by simply asking "do you feel hopeless?" The GDAS energy item was selected because it was phrased to indicate a deficit in energy (as opposed to feeling full of energy).

We assessed the age- and site-adjusted associations of all covariates with LCA group using multi-nominal logistic regression. The reference group was also set to be the group that appeared most healthy (i.e. by not having sleep or depression symptoms). Items included as LCA indicators were not eligible predictors of the derived classes (i.e. GDS was not an eligible predictor of depression LCA group membership). Otherwise, all significant crude associations ($p<0.10$) were entered into a maximum model, and automated backwards elimination in SAS was used to select predictors retaining adjusted significance of at least $p<0.15$. Multicollinearity was assessed using the variance inflation factor (VIF). The selected independent predictors were entered into a final multi-nominal logistic model within the PROC LCA framework, thus ensuring that no measurement error was introduced. In these final models, we applied a data-

derived prior to stabilize estimates of item-response probabilities (sleep, CARs, and depression models) and regression parameters (only sleep and depression models).

The final model included cross-sectional predictors which were assessed in only a sub-set of the MrOS Sleep Study (inflammatory marker and PSG studies). We therefore re-performed LCA model selection among the subset with complete covariate data. In all domains, the prevalence and characteristics of identified sub-groups were similar in the reduced models (missing covariate data, minimum reduced n=2473) compared with the full sample.

2.3 RESULTS

2.3.1 Sleep LCA

2.3.1.1 Description and prevalence of latent sleep classes

Subjective and objective (actigraph) measured sleep variables were best fit by a five group model (Table 4). For consistency with correlates tables, all LCA analyses are shown in item-response probability plots corresponding to the final model (participants with complete covariate data). Figure 2 shows indicator items across the x-axis with the conditional item response probability on the y-axis. Descriptive sleep characteristics (Table 5) indicate that item-response probabilities corresponded to real, substantial group differences in these sleep disturbances.

The majority of participants (45.17%) had a low probability of endorsing any symptom (“healthy sleep”). Substantial portions had high probabilities of endorsing either the single item

"Have you been waking early?" (25.57%) or all subjective sleep disturbance items except weekly excessive daytime sleepiness (11.89%). One group had objective sleep disturbances (8.51%) as indicated by high probabilities of actigraph assessed sleep fragmentation (WASO≥90 minutes) and intermediate probabilities of both short (<5 hour) sleep and prolonged SL (≥60 minutes). The remaining group (8.87%) had a similar pattern of sleep disturbances as the "subjective only" and "objective only" groups, except that this portion of the sample had both sets of elevated sleep disturbance probabilities.

2.3.1.2 Correlates of latent sleep classes

Age- and site-adjusted odds for all covariates indicated a number of cross-sectional associations with LCA-depression groupings (all comparisons are to the reference group of apparently healthy sleepers; Table 6).

In the final model (Table 7), moderate alcohol use was marginally associated with (13%) *higher* odds of being the objective disturbance only group but also with 12% *lower* odds of being in the subjective and objective disturbance group. Moderate alcohol consumption was significantly associated with 19% decreased odds of being in the subjective disturbance group. Being a current smoker was related to over twice the odds of having objective sleep disturbances alone, while being a former smoker was related to 17% higher odds of having both subjective and objective sleep disturbances.

Higher BMI was related to increased odds of being in either group with objective disturbances (15% and 26%). Anxiety symptoms were related to about 55% higher odds (per standard deviation) of being in the groups with subjective disturbances, and anxiety was related to 16% higher odds of being in the early awakening only group.

Each additional IADL impairment was related to 20% higher odds of being in the group with both subjective and objective disturbances only; higher TNF-α was related to 25% higher odds of being in this group (marginally significant finding). On the other hand, higher levels of TNF-α were related to modestly (16%) lower odds of being in the "early awakenings" group.

OA was related to 22% increased odds of being in the objective disturbances alone group. CHF was related to 42% and 46% higher odds, respectively, of being in the subjective plus objective and objective alone group. Severe SDB were related to about 18% and 36% higher respective odds of being the objective plus subjective and objective disturbances alone groups.

Antidepressant use was marginally associated with 22% higher odds of being in the objective disturbance group. Non-benzodiazepine non-barbiturate sedatives/hypnotic use was associated with over twice the odds of being in the groups with multiple subjective sleep complaints; benzodiazepine use was associated (30% higher odds) with being in the subjective disturbances alone group. NSAID use was associated with 22% and 30% higher odds of being in the groups with multiple subjective sleep disturbances, and this association with being in the early awakening group was marginally significant.

2.3.2 *CAR LCA*

2.3.2.1 Description and prevalence of latent CAR classes

Circadian rhythm variables were best modeled using eight groups (Table 8; Figure 3). Groups were labeled and their characteristics are describe in Table 11. The largest group had apparently normal rhythms as indicated by low probabilities of being in any extreme quartile (32.18%). A group had a high probability of low mesor and amplitude with an intermediate

probability of low robustness (“reduced activity,” 9.79%), but lower probabilities of having standardized amplitude and low probabilities of non-normative timing.

Two groups appeared to have non-normative timing alone: one group had earlier peaks and up-mesors plus an intermediate probability of an earlier down-mesor (“early activity’; 10.7%). Another group had later peaks and down-mesors with an intermediate probability of a later up-mesor (“late activity”; 14.36%).

Two groups had altered timing and active period length. Of these groups, one had an earlier peak and down-mesor combined with a high alpha (“early activity with short active period”; 10.54%). Another group had a later up-mesor with a short active period (“late rising with short active period”; 8.27%).

The final two groups had similarly advanced or delayed activity as above, except that these last groups also had high probabilities of altered rhythm height/robustness. One group had high probabilities of having an advanced peak and settling time (down-mesor) with a shorter active period, plus high probabilities of having low height, standardized amplitude, and robustness period (“early, dampened rhythm with short active period”; 6.48%). The last group had delayed CAR activity plus a high probability of low height/robustness (“late with reduced activity”; 7.68%).

Examining continuous characteristics for each CAR parameter by group demonstrates substantial mean differences consistent with the conditional item response probabilities (Table 9). For descriptive purposes, we show also correlations between continuous CAR parameters (Table 10).

2.3.2.2 Correlates of latent CAR classes

In the final model (Table 13), older age was independently associated with about 38% higher odds of being in the "reduced activity" and "early, dampened rhythm with short active period" groups (all comparisons are with being in the "normative rhythm" group). Note that in the unadjusted models (Table 12), advanced age was also associated with higher odds of being in the "late with reduced activity" group; thus, the relationship between age and this group appears to be accounted for by the factors included in the final model.

Alcohol use was associated with lower odds of being in the "late with reduced activity" group (both in unadjusted and adjusted models). The final model also indicated that drinking 14+ alcoholic beverages per week (vs.<1 drink/week) was associated with higher odds of being in the "early activity with short active period" or "late activity with short active period" groups; however, these associations were not detected in the unadjusted models (Table 12).

Higher education was associated with significantly decreased odds of being in the late peak/down mesor group. Being a current smoker was associated with over three times the odds of being in the "early activity with short active period" group. Higher BMI was associated with higher odds of being in all groups with indication of reduced locomotor activity, as well as higher odds of being in the "late rising with short active period" group.

Higher levels of self-reported physical activity were associated with lower odds of being in all groups with indication of reduced locomotor activity, as well as reduced odds of being in the "late activity" group. Anxiety symptoms were marginally and modestly associated with being in the "late with short active period" group. Higher cognitive functioning scores were associated (per standard deviation) with about 20% lower odds of being in the "late rising with short active period" and "early, dampened rhythm with short active period" groups.

IADL impairments were related to higher odds of being in all of the disturbed (vs. normal rhythm) groups except for the "early activity with short active period" group. Hypertension was related to higher odds of being only in the "early, dampened rhythm with short active period group." CHF and COPD were related to higher odds of being in the "reduced activity" group only, whereas MI was related to higher odds of being in the "late rising with short active period" group.

Levels of CRP were positively related to the odds of being in the "reduced activity," "early activity with short active period," "late rising with short active period," and both group with altered timing plus activity reductions; note that in the adjusted models, CRP levels were also associated with the altered timing only groups. Levels of TNF-α were positively associated with the odds of being in the "early activity" or "late activity" alone groups; in the unadjusted models, TNF-α was positively related to all groups except those with altered timing plus a shortened period.

2.3.3 *Depression LCA*

2.3.3.1 Description and prevalence of latent depression classes

When combining GDS data with items selected from the other depression scales (Table 14), BIC indicated a five group solution fit the data best (Table 15). The final LCA solution in the sub-set of participants with complete covariate data is shown graphically (Figure 4). The largest group identified appeared to be free of symptoms (53.86%; "not depressed"). The second largest group (27.70%; "probable somatic/ apathy") had low probabilities of most symptoms indicating a general lack of depression symptoms; however this group had intermediate to high probabilities of endorsing somatic symptoms (especially "feeling slowed") and had some

indication of apathy (i.e. “prefer home”). A parallel group (5.74%; “probable somatic/apathy with impairment”) had approximately the same pattern of symptom expression but also had high probabilities of endorsing impairment indicators, especially accomplishing ‘less than they would like’ due to emotional issues.

The final two groups, in addition to having the high probabilities of somatic and apathy symptoms, had non-zero probabilities across the entire range of cognitive/psychological symptoms. One of these groups (“apathy/somatic w/probable impairment”; 8.45%) had a low probability of feeling hopeless, worthless, or empty, but had intermediate probabilities of the following symptoms: cognitive/memory problems, social withdrawal, irritability, anhedonia, and impairment. The last group (4.25%) had intermediate to high probabilities across the entire range of cognitive/psychological symptoms; this group also had a high probability of endorsing impairment and is accordingly referred to as the “depressed” group.

Descriptive mental health characteristics indicate that the two groups with probable somatic/apathy symptoms were similar in mean number of depression and anxiety symptoms but different in terms of the percentage with emotional impairment (Table 16). As expected, the depressed group had the highest levels of depressive symptomology, followed by the “apathy/somatic with probable impairment” group; the two groups with probable somatic/apathy syndromes experienced, on average, about two depression symptoms.

2.3.3.2 Correlates of latent depression classes

Age- and site-adjusted odds for all covariates indicated a number of cross-sectional associations with LCA-depression groupings (compared to the reference group “not depressed”) (Table 17). Significant associations ($p<.10$) were entered into a maximum model and associations which retained independent significance were entered into the final model.

In this final model (Table 18), older age and low CAR amplitude had modest, independent associations with increased odds of being in both the “apathy/somatic w/ probable impairment” and “probable somatic/apathy” groups; early up-mesor was also significantly associated with decreased odds of being in these two groups. Late-down mesor was associated with 46% higher odds of being in the “depressed” group.

Higher levels of anxiety symptoms and worse global sleep quality were associated with being in all groups (relative to the non-depressed reference); the strength of this association was greatest for the “depressed” group (over twice the odds vs. “not depressed”), followed by the group with apathy/somatic symptoms (56% higher odds), the group with probable apathy/somatic symptoms with impairment (32% higher odds), and anxiety was only modestly (10% higher odds) associated with being in the probable somatic/apathy group without impairment .

Higher physical activity scores were modestly related to decreased odds of being in all groups except “probable somatic/apathy w/ impairment.” Daytime sleepiness and IADL impairment were also associated with modestly increased odds of being in all groups except “probable somatic/apathy w/ impairment.” This same pattern (associated with higher odds of being all depression groups except “probable somatic/apathy w/ impairment”) was observed for past year falls and stroke; however these associations were graded such that the odds were most increased for the “depressed” group (also note that the association between stroke being in the “apathy/somatic w/probable impairment” group was only marginally significant).

Peripheral vascular disease was associated with 18-36% increased odds of all groups except “depressed.” Rheumatoid arthritis was associated with 28 and 48% increased odds of being in the “depressed” and “apathy/somatic w/ probable impairment” groups, respectively.

COPD was associated with 57 and 25% higher odds of being in the “depressed” or “probable somatic/apathy” groups, respectively. Cataracts were associated with marginally reduced odds of being in the “probable somatic/apathy w/ impairment” group.

Higher CRP levels were significantly associated with 16% higher odds of membership in the “probable somatic/apathy w/ impairment” group. TNF-αsRII was significantly associated with 26% higher odds of being in the “probable somatic/apathy” group.

2.4 DISCUSSION

Findings are summarized and discussed by domain followed by an overall discussion.

2.4.1.1 Summary of sleep LCA and correlates

Consistent with our hypothesis, we observed that a substantial portion of older men in the MrOS Sleep Study reported subjective sleep disturbances (11.9% reported multiple subjective disturbances). We did not, however, anticipate the dramatic dissociation observed between subjective and objective disturbances: while almost 20% had evidence of either type of sleep disturbance, only about 9% had both.

This novel finding highlights the importance of measuring both perceived and objectively measured sleep quality. About 11% of older men may have objective sleep disturbances which would not have been detected using self-report. Since these objective disturbances may be risk factors for future disease (i.e. falls [170] or dementia [171]), routine clinical use of actigraph may be necessary to identify sleep risk factors among older men.

We also found that long sleep duration did not tend to co-occur with greater sleep fragmentation or prolonged sleep latency. Instead, short sleep was more often accompanied by these objective disturbances. Thus, in our sample, actigraph detected night-time distress is typically characterized by sleep fragmentation which is potentially accompanied by short sleep and/or prolonged sleep latency.

Unanticipated, though consistent with known clinical observations, a substantial portion of the sample reported early awakening alone. This group did not appear to be distinguished from the healthy sleepers (45.17%) by chronic illness. Anxiety symptoms were related to higher odds while TNF-α levels were related to lower odds of having early awakenings only (compared with the healthy sleeper group). Although future research is required produce definitive evidence, our findings suggest that reports of early awakening without other sleep disruption may be marked by mild anxiety despite having relatively lower levels of this sub-clinical disease marker.

Moderate alcohol consumption was associated with reduced odds of being in either subjective sleep disturbance group, but increased odds of having objective disturbances alone; this finding suggests a potential dubious role of moderate alcohol consumption among older men. Anxiety symptoms were related to being in either group with subjective disturbances, whereas CHF and SDB were related to being in either group with objective disturbances; these findings suggest a mental origin to subjective disturbances, and a physical origin to objective disturbances.

Interestingly, sedative/hypnotic use was associated with being in either group with multiple subjective complaints. Because this data is both observational and cross-sectional, a strong possibility is that sedative/hypnotics were prescribed *for the subjective complaints*

(confounding by indication). Either sedative/hypnotic use actually caused subjective sleep disturbances, or they were prescribed for the sleep complaint but were inefficacious. It may be that the group with subjective disturbances alone at one point suffered from objective disturbances, but by time of study the sedative/hypnotic prescription produced objectively measurable improvements in sleep (only in this subset). Even in this case, our findings still demonstrates sedative/hypnotics use is related to a higher prevalence of subjective sleep complaints, and other treatment strategies are urgently needed for these problems.

The high prevalence of dissociation between subjective and objective sleep complaints calls for cautious interpretation of self-reported sleep. Subjective complaints are still important in their own right. Clinical research is needed to test the efficacy of sedative/hypnotics in reducing distinct (subjective/objective) types of sleep disturbances, and potentially to establish other (i.e. behavioral) interventions to resolve mental suffering related to poor sleep perceptions. Finally, future research is required to determine the physical, perhaps electrophysiological underpinnings involved in the development of poor perceived sleep, as well as in the characterization of sleep phenotypes overall. Given the high prevalence and stark disassociation of subjective and objective sleep disturbances, sleep medicine should consider routine use actigraph to complement self-report.

Future studies are needed to determine if a similar dissociation of subjective and objective disturbances is observed in other samples. Future longitudinal studies are needed to assess the development, stability, and long term consequences of these latent groups.

2.4.1.2 Summary of CAR LCA and correlates

Application of LCA to a range of CAR disturbances produced intuitive but novel insights into the common CARs patterns occurring among community dwelling older men. Contrary to

our hypothesis, rhythm robustness was not a unique factor which distinguished CAR groups; instead, a lack of rhythm robustness appeared in the presence of overall reductions in locomotor activity (unstandardized rhythm height parameters mesor and amplitude). Therefore, a lack of rhythm robustness may directly precede or result from overall locomotion reduction, and future longitudinal research is needed to assess these relationships. Because rhythm robustness has previously been associated with health outcomes when rhythm height measures themselves were not [115], it may still be that low CAR robustness reflects a distinct process that emerges from or entails overall locomotor reductions.

Timing variables distinguished CAR patterns in our sample intuitively, i.e. into "larks" or "owls". After accounting for effects of lifestyle and chronic disease factors, higher levels of TNF-α were only uniquely associated with having both advanced or delayed timing only (i.e. without altered locomotor levels or periods). TNF-α may be thus particularly related to altered activity timing; although this cytokine exhibits diurnal variation [172], morning fasting blood samples were drawn and detecting relations to *both* advances and delays negates potential confounding by time of draw. Unadjusted associations between TNF-α with the other sub-groups were attenuated after adjustment; therefore, the measured health factors explained these associations. But outside from IADL impairment, chronic diseases were not associated with the odds of having only an altered phase (timing). Therefore, having altered timing alone may be characterized by disability and subclinical disease.

Having a more narrow active period emerged as a distinguishing characteristic of three latent sub-groups. Lifestyle factors may have a particularly important role conferring certain combinations of timing and activity alterations. Men with less education were relatively unlikely to have late timing without altered activity levels/periods. Current smoking and heavy (14+

drinks per week) alcohol consumption was related to having an early and compressed CAR. Current smoking was also associated with having delayed timing plus locomotor reductions, and heavier alcohol consumption was also associated with having late timing with a shortened active period. Levels of CRP were also positively associated with these group, and indeed, were positively associated with being in any groups that had a shortened active period or activity reductions. CRP is a downstream product of the liver that does not cross the blood brain barrier [173], thus associations between CRP and locomotor compression/reductions likely indicate systemic disease processes rather than a direct causal effect from CRP to disruption of the central circadian clock.

Two groups had altered timing plus reductions in locomotor activity. Hypertension was associated with higher odds of earlier timing plus dampened rhythm with a shorter activity period. Because these are cross-sectional associations, we cannot assess causality and future research is necessary to assess the causes and consequences of these CAR configurations. However, it is worth highlighting that, overall, physical disease appeared to be highly associated with being in the non-normative (disturbed) CAR groups; for example, CHF and COPD were strongly associated with having locomotor reductions.

It is also important to note that IADL impairment was widely related to having a disturbed CAR, especially late timing plus altered activity (levels or period). A role of IADL impairment in the development of disturbed CARs is both intuitive and suggested by our findings. Therefore, studying disability in general is a high priority for future research investigating the development of altered CARs.

2.4.1.3 Summary of depression LCA and correlates

Consistent with our hypothesis, psychological/cognitive symptoms were less common when compared with the high prevalence of syndromes characterized by somatic/apathy symptoms alone. Importantly, we found that impairment (difficulty accomplishing as much as they would like due to emotional issues) occurred not only among those with a higher burden of psychological, cognitive, and apathy symptoms, but within a sub-set (5.74/33.44%) of those with probable somatic/apathy symptoms alone.

Examining the cross-sectional correlates of latent group membership suggest relevant causes or consequences of these depressive symptom configurations that should be examined in future longitudinal research. Several correlates of both the "probable somatic/apathy and "depressed" group differed in strength of association such that these factors (physical activity, anxiety, past year falls, stroke, and COPD) were more robustly associated with the group having more general and severe depression symptoms. These, in addition to anxiety symptoms and subjective sleep disturbances, appear to be general correlates of the range of depressive syndromes identified.

For example, the following factors increased the odds being in the "depressed" group: more anxiety symptoms, subjective sleep disturbances, later evening settling times, more IADL impairments, a past year fall, rheumatoid arthritis, stroke, and COPD. The odds of being in the group with a near-definite apathy/somatic syndrome that had a substantial probability of impairment were increased by: older age, anxiety symptoms, worse subjective sleep quality, lower levels of locomotor activity, IADL impairment, past year fall, peripheral vascular disease, and rheumatoid arthritis. Differences in the unique correlates of these sub-groups ("depressed" vs. "apathy/somatic") may generate hypotheses regarding the development of specific

syndromes. For example is severe peripheral vascular disease uniquely involved in the development of apathy symptoms, whereas cerebrovascular and pulmonary disease risk factors are more generally related depression? Importantly, eliminating these correlated physical health problems may help relieve the major burden of depression found among older men.

The overall the pattern of covariate association was similar for the probable somatic/apathy group without impairment group when compared with the both of the more severe syndromes. Some differences should be noted: rheumatoid arthritis, although related to both the "depressed" and "apathy/somatic with probable impairment" groups, was not related to higher odds of being in the milder "probable somatic/apathy" groups. However, TNF-αsRII was uniquely associated with being in the "probable somatic/apathy without impairment" group. Significant age- and site- adjusted relationships of TNF-αsRII with higher odds of being in the "depressed" and "apathy/somatic with probable impairment" groups were attenuated in the final model by covariates adjustments; thus, overt disease may explain associations between TNF-αsRII and more severe depression, whereas higher levels of subclinical disease marked by TNF-αsRII may be particularly involved in the experience of mild somatic/apathy depression without emotional impairment.

Interestingly, the "probable somatic/apathy with impairment" group lacked associations with almost all of the above discussed other groups' correlates. Higher levels of anxiety symptoms, worse global sleep quality, and peripheral vascular disease were associated with higher odds of membership in the "probable somatic/apathy with impairment" group. However, levels of physical activity, daytime sleepiness, IADL impairment, past-year falls, stroke and COPD (which were noted as correlates of the other syndromes) were not associated with membership in this potentially important subgroup.

CRP levels, although not associated with any of the other groups in the final model, were positively associated with having only probably somatic/apathy symptoms plus impairment. In unadjusted models, CRP levels were also associated with higher odds of membership in other depressed sub-groups (vs. not depressed); in the final model, it is likely that overt chronic diseases (discussed above) explain associations between CRP and these sub-group. However, only peripheral vascular disease and CRP levels were uniquely associated with being in the group with emotional impairment alongside only a few symptoms; these are likely important markers of the physical factors related to this sub-group. Again note that CRP is a downstream product of the liver that does not cross the blood brain barrier [173], and thus CRP is likely a consequence (not a cause) of factors related to being in the "probable somatic/apathy plus impairment" group.

In sum, a substantial minority experienced at least probable somatic and/or apathy symptoms. These symptoms may be caused by complex relations between reduced physical activity, poor subjective sleep quality, anxiety, and physical disease. Peripheral vascular disease, arthritis, and either overt or subclinical inflammatory-related disease appear to be particularly relevant physical health correlates. Patterns of symptoms consistent with a MDD diagnosis were relatively rare (about 5%), although emotional impairment was at least twice as common. Researchers and clinicians may thus benefit from evaluating emotional impairment even among older adults without psychological complaints. Future work should account for the severity of individual symptoms rather than their presence or absence explains individual variability in emotional impairment.

2.4.1.4 Overall conclusions

Prior epidemiologic sleep and depression research tends to reference known disease entities to produce prevalence estimates of: (1) known disorders, (2) symptomatic but sub-threshold syndromes, and (3) healthy states. Our investigation provides more detail into the nature of sub-threshold syndromes. We found that only 53.86% of our sample was free from some type of probable depressive syndrome, only 45.17% had no sleep disturbances, and only 32.18% had all normative CAR parameters. In the case of depression, variability was characterized, not just by total symptom count, but also by symptom expression. Specific dissociations between sub-groups in the sleep and CAR domains were also dramatic and intuitive.

Future work is needed to investigate the development, stability, and consequences of the identified syndromes. A short-term research priority is to investigate the natural history and risk relations pertaining to the specific signs/symptoms which appeared valuable in discriminating specific sub-groups (i.e. early morning awakening, activity period compression, or emotional impairment). It is crucial for future research to assess whether similar sub-groups can be identified among other samples. It may be that some of the identified groups are sample specific, owing to nuances of our study's design or age group.

A major limitation of the current work is the cross-sectional design which excluded analysis of the temporal antecedents or consequences of the sub-groups identified. The roles of genetic and environmental factors in these relations must also be examined. In addition, the sample was mostly white, relatively educated men who were older; these findings should not be generalized to the younger adults, women, or some ethic groups. The final models included only participants with complete covariate data which required the somewhat more invasive PSG and

inflammatory marker measures; nevertheless, the same LCA groupings were identified in this sub-set when compared with the groups found among the entire sample. Still, the external validity of the study is limited and future studies should attempt to confirm our findings in other samples.

All sign/symptom indicators were coded as binary variables reflecting the presence or absence of a specific disturbance, but the severity of each sign/symptom was not accounted for. Examining descriptive characteristics in each group (i.e. mean WASO, acrophase, or depressive symptom levels) provides assurance the groups were distinct and our examination of pre-defined disturbances supported enhanced interpretability. Nonetheless, future latent profile research with continuous disease indicators may shed important light on heterogeneity in health/disease states.

In sum, we found substantial heterogeneity in sleep, CAR, and depressive symptoms. Sub-diagnostic syndromes are common and potentially clinically significant. Disability, vascular, and pulmonary disease factors appeared to characterize worse disease states across domains. It remains true that clinically-derived diagnostic categorizes have an essential roles ensuring clinical relevance and fostering improved care for patients with a known disorder; nevertheless, we have provided preliminary evidence that data-driven research has the potential to improve our understanding of new or under-recognized syndromes. Indeed, this approach of studying naturally occurring configurations of signs/symptoms can complement other approaches and provide evidence for refining nosology, especially in new areas of study like the CAR. The current cross-sectional analysis provides a basis for future longitudinal research on the long-term consequences of these sub-diagnostic disease states.

2.5 TABLES AND FIGURES

Table 4. BIC for different number of latent classes using all sleep indicators

Number of latent classes	Log likelihood	BIC	Entropy
1	-11858.18	3459.51	1.00
2	-10685.10	1193.42	0.90
3	-10426.09	755.48	0.83
4	-10386.21	755.79	0.87
5	**-8552.22**	**652.90**	**0.84**
6	-8539.85	711.78	0.78

BOLD solution selected

Table 5. Descriptive sleep characteristics of sleep latent classes (% (n) unless otherwise noted)

Name of latent class	Daytime sleepiness	Early Awakening	Poor sleep	Low sleep quality	Difficulty falling asleep	SL, mean minutes (sd)	WASO, mean minutes (sd)	TST, mean minutes (sd)	>8 hours TST	<5 hours TST
Healthy sleep	3.46 (47)	0 (0)	2.88 (39)	1.47 (20)	4.20 (57)	22.99 (16.78)	68.15 (35.45)	407.95 (57.56)	9.71 (132)	1.19 (26)
Early awakening	6.52 (53)	100 (813)	15.38 (125)	1.72 (14)	5.17 (42)	22.29 (15.07)	67.98 (34.51)	392.33 (55.40)	5.42 (44)	3.82 (31)
Subjective dist.	11.24 (47)	79.86 (333)	99.52 (415)	73.92 (309)	69.30 (289)	25.13 (16.42)	71.11 (33.95)	397.41 (61.22)	9.35 (39)	4.56 (19)
Objective dist.	9.45 (24)	37.80 (96)	0 (0)	1.97 (5)	7.48 (19)	79.64 (56.41)	137.33 (47.20)	268..33 (64.34)	0 (0)	77.56 (197)
Subjective and objective dist.	11.95 (19)	57.86 (92)	94.97 (151)	74.84 (119)	67.30 (107)	78.40 (57.74)	146.52 (45.77)	295.04 (90.52)	0.63 (1)	61.64 (98)

All variables coded as indicated in text on sleep LCA methods; dist. = disturbance; sd = standard deviation

Table 6. Age and site adjusted odds of membership in LCA-derived sleep subgroups (vs. healthy sleepers, 45.17%)

	Subjective and objective disturbances (8.87%)	Objective disturbances (8.51%)	Subjective disturbances only (11.89%)	Early awakenings only (25.57%)
Age (per SD)	1.26 (1.07-1.48)	1.08 (0.94-1.24)	1.04 (0.93-1.17)	1.05 (0.96-1.14)
Study Site (vs. PI):				
BI	0.58 (0.35-0.96)	0.34 (0.21-0.55)	0.89 (0.61-1.29)	0.80 (0.59-1.09)
MN	0.40 (0.23-0.67)	0.47 (0.31-0.72)	0.72 (0.49-1.04)	0.76 (0.56-1.02)
PA	0.18 (0.10-0.36)	0.33 (0.21-0.53)	0.67 (0.46-0.98)	0.74 (0.54-1.00)
PO	0.38 (0.21-0.66)	0.53 (0.34-0.83)	0.70 (0.47-1.04)	0.82 (0.60-1.12)
SD	0.44 (0.26-0.73)	0.53 (0.35-0.80)	0.65 (0.44-0.95)	0.78 (0.58-1.05)
Race:				
Black vs. White	2.28 (1.14-4.60)	1.55 (0.80-3.00)	0.87 (0.47-1.59)	0.81 (0.49-1.33)
Other vs. White	2.78 (1.44-5.36)	0.96 (0.49-1.87)	1.39 (0.87-2.21)	1.48 (1.03-2.12)
Alcohol use per week:				
1-13 drinks vs. <1 drink	0.75 (0.52-1.07)	1.24 (0.93-1.65)	0.65 (0.52-0.83)	0.94 (0.78-1.13)
14+ drinks vs. <1 drink	1.31 (0.68-2.54)	1.08 (0.57-2.02)	0.70 (0.42-1.18)	1.05 (0.71-1.54)
Daily caffeine intake (per SD)	1.16 (0.99-1.35)	1.09 (0.96-1.24)	0.93 (0.83-1.05)	1.08 (0.99-1.18)
Education:				
Less than high school vs. College/graduate school	2.55 (1.42-4.56)	1.36 (0.75-2.48)	1.62 (1.00-2.61)	1.28 (0.83-1.95)
High school diploma vs. College/graduate school	1.30 (0.83-2.05)	1.19 (0.82-1.74)	1.06 (0.76-1.47)	1.36 (1.06-1.76)
Smoking Status:				
Former vs. None	2.03 (1.39-2.95)	1.24 (0.93-1.64)	1.08 (0.86-1.36)	1.03 (0.86-1.23)
Current vs. None	1.90 (0.54-6.72)	2.79 (1.26-6.17)	1.06 (0.45-2.55)	1.24 (0.64-2.41)
BMI (per SD)	1.63 (1.40-1.91)	1.68 (1.48-1.92)	1.10 (0.98-1.24)	0.98 (0.89-1.08)
Physical Activity (per SD)	0.74 (0.61-0.89)	0.89 (0.77-1.03)	0.84 (0.74-0.94)	1.09 (1.00-1.19)
Cognitive function (per SD)	0.78 (0.67-0.90)	0.93 (0.80-1.07)	0.86 (0.77-0.96)	0.92 (0.83-1.00)
Anxiety symptoms (per SD)	2.82 (2.43-3.26)	1.21 (0.99-1.47)	2.60 (2.31-2.93)	1.56 (1.39-1.76)
Depressive symptoms (per SD)	2.04 (1.78-2.33)	1.26 (1.08-1.47)	1.81 (1.62-2.02)	1.30 (1.17-1.44)
Chronic Disease History				

Table 6 continued

IADL impairment (per additional)	1.85 (1.59-2.15)	1.31 (1.11-1.53)	1.49 (1.32-1.69)	1.04 (0.91-1.18)
Fall in past 12 months	1.99 (1.42-2.79)	1.33 (0.99-1.77)	1.24 (0.98-1.57)	0.96 (0.79-1.17)
Peripheral vascular disease	1.61 (0.99-2.60)	1.14 (0.73-1.77)	1.35 (0.95-1.92)	1.01 (0.74-1.37)
Osteoarthritis	2.38 (1.67-3.38)	1.86 (1.38-2.51)	1.84 (1.44-2.36)	1.02 (0.82-1.27)
Rheumatoid Arthritis	2.16 (1.33-3.52)	1.10 (0.66-1.82)	1.84 (1.29-2.64)	0.93 (0.66-1.32)
Hypertension	1.69 (1.21-2.37)	1.24 (0.95-1.62)	1.31 (1.05-1.64)	1.10 (0.93-1.31)
Stroke	1.83 (0.92-3.61)	0.64 (0.27-1.51)	0.77 (0.42-1.43)	0.80 (0.50-1.30)
Angina	1.79 (1.20-2.66)	1.23 (0.85-1.76)	1.31 (0.97-1.75)	0.87 (0.68-1.13)
Congestive Heart Failure	3.33 (1.94-5.72)	3.03 (1.89-4.86)	1.69 (1.06-2.71)	1.41 (0.94-2.10)
Myocardial Infarction	1.94 (1.32-2.85)	1.39 (0.98-1.97)	1.57 (1.19-2.07)	1.09 (0.86-1.39)
Diabetes	1.57 (1.01-2.43)	1.63 (1.13-2.33)	1.11 (0.80-1.54)	1.16 (0.89-1.50)
COPD	2.08 (1.14-3.81)	1.77 (1.03-3.07)	1.54 (0.96-2.48)	1.25 (0.83-1.89)
Parkinson's	3.08 (0.99-9.59)	1.37 (0.39-4.83)	1.95 (0.81-4.70)	0.86 (0.35-2.14)
Renal disease	1.30 (0.37-4.54)	0.59 (0.14-2.58)	0.89 (0.33-2.41)	0.45 (0.17-1.23)
Cataracts	1.34 (0.95-1.89)	1.06 (0.80-1.41)	1.25 (0.99-1.56)	1.18 (0.98-1.41)
Liver disease	1.01 (0.30-3.38)	0.57 (0.17-1.90)	1.24 (0.61-2.49)	0.74 (0.38-1.42)
Severe SDB (AHI $\geq$ 30)	2.25 (1.53-3.32)	2.43 (1.76-3.36)	1.03 (0.75-1.41)	1.06 (0.83-1.37)
<u>Medication Use</u>				
Antidepressant use	2.06 (1.25-3.40)	1.57 (1-2.47)	1.59 (1.10-2.30)	0.74 (0.52-1.08)
Non-benzodiazepine non-barbiturate sedatives/hypnotics	7.03 (2.91-17.00)	1.46 (0.41-5.20)	6.74 (3.40-13.33)	1.32 (0.57-3.02)
Benzodiazepines use	3.00 (1.64-5.51)	0.98 (0.45-2.11)	3.35 (2.17-5.17)	0.77 (0.45-1.30)
Current NSAID use	1.90 (1.30-2.77)	1.04 (0.73-1.48)	1.87 (1.44-2.41)	1.15 (0.92-1.44)
Current corticosteroid use (oral/nasal/inhaled)	1.65 (1.02-2.67)	1.02 (0.65-1.61)	0.88 (0.59-1.30)	0.86 (0.63-1.17)
<u>Inflammatory Markers</u>				
log(IL-6 + 1)	1.37 (0.97-1.94)	1.72 (1.32-2.23)	1.15 (0.88-1.49)	1.01 (0.81-1.26)
log(CRP + 1)	1.50 (1.17-1.93)	1.28 (1.02-1.60)	1.14 (0.95-1.37)	0.99 (0.85-1.15)
log(TNF-α + 1)	2.36 (1.25-4.48)	1.58 (0.91-2.73)	1.05 (0.67-1.65)	0.72 (0.50-1.03)
log(TNF-αsRII + 1)	1.81 (1.09-3.02)	1.36 (0.88-2.10)	1.36 (0.96-1.93)	0.78 (0.58-1.03)
log(IFN-γ + 1)	1.08 (0.81-1.45)	0.89 (0.69-1.15)	0.96 (0.79-1.18)	0.87 (0.74-1.02)

*Crude associations adjusted for age and study site

Table 7. Final model (n=2515) showing adjusted odds (95% confidence interval) of membership in LCA-derived sleep subgroups (vs. healthy sleepers, 43.42%)

	Subjective and objective disturbances (8.87%)	Objective disturbances (8.51%)	Subjective disturbances only (11.89%)	Early awakenings only (25.57%)
Age (per SD)	1.05 (0.98-1.12)	1.06 (0.99-1.12)	0.99 (0.93-1.04)	1.03 (0.98-1.08)
Alcohol use per week:				
1-13 drinks vs. <1 drink	0.88 (0.76-1.00)	1.13 (1.00-1.27)	0.81 (0.73-0.91)	0.98 (0.90-1.07)
14+ drinks vs. <1 drink	0.92 (0.68-1.25)	1.08 (0.82-1.40)	0.85 (0.66-1.08)	0.97 (0.80-1.17)
Smoking Status:				
Former vs. None	1.17 (1.02-1.34)	1.07 (0.95-1.21)	0.96 (0.86-1.07)	1.01 (0.92-1.10)
Current vs. None	1.11 (0.67-1.83)	2.21 (1.55-3.15)	1.17 (0.80-1.73)	0.95 (0.68-1.33)
BMI (per SD)	1.15 (1.08-1.23)	1.26 (1.18-1.33)	1.01 (0.95-1.07)	1.00 (0.95-1.04)
Anxiety symptoms (per SD)	1.56 (1.47-1.65)	1.04 (0.97-1.11)	1.55 (1.48-1.63)	1.16 (1.10-1.21)
Chronic Disease History				
IADL impairment (per additional)	1.20 (1.11-1.29)	1.06 (0.98-1.14)	1.03 (0.96-1.10)	1.00 (0.94-1.06)
Osteoarthritis	0.98 (0.84-1.14)	1.22 (1.07-1.40)	1.09 (0.96-1.23)	0.90 (0.81-1.00)
Congestive Heart Failure	1.42 (1.10-1.82)	1.46 (1.17-1.84)	1.03 (0.81-1.31)	1.14 (0.94-1.38)
Severe SDB (AHI $\geq$ 30)	1.18 (1.00-1.39)	1.36 (1.18-1.57)	0.97 (0.84-1.13)	1.00 (0.89-1.12)
Medication Use				
Antidepressant use	0.85 (0.67-1.08)	1.22 (0.99-1.51)	0.97 (0.81-1.18)	0.85 (0.72-1.01)
Non-benzodiazepine non-barbiturate sedatives/hypnotics	2.19 (1.48-3.24)	1.29 (0.83-2.02)	2.38 (1.74-3.25)	1.09 (0.79-1.52)
Benzodiazepines use	1.22 (0.93-1.60)	0.82 (0.61-1.11)	1.30 (1.04-1.64)	0.83 (0.66-1.04)
Current NSAID use	1.30 (1.11-1.52)	0.99 (0.85-1.15)	1.22 (1.07-1.39)	1.11 (1.00-1.24)
Inflammatory Markers				
log(TNF-α + 1)	1.25 (0.99-1.59)	1.16 (0.94-1.44)	0.90 (0.74-1.09)	0.84 (0.71-0.98)

Estimates also adjusted for study site

Table 8. BIC for different number of latent classes using all CAR indicators

Number of latent classes	Log likelihood	BIC	Entropy
1	-17800.07	9674.18	1.00
2	-16407.27	6984.67	1.00
3	-15482.09	5230.40	0.93
4	-15142.20	4646.71	0.94
5	-14435.54	3329.48	0.98
6	-14219.98	2994.45	0.95
7	-13860.36	2371.30	0.95
8	**-13596.55**	**1939.79**	**0.95**
9*	-13563.15	1969.07	0.91

BOLD solution selected ; *=included non-distinct groups of <5% of the sample

Table 9. Descriptive characteristics of CAR latent classes, mean (SD)

Name of latent class	Acrophase	Up-mesor	Down-mesor	St. Amp.	Mesor	Amp.	Pseudo-f	Alpha
Normal rhythm	14.29 (0.39)	6.71 (0.61)	21.86 (0.68)	1.78 (0.19)	2234.51 (329.52)	3953.75 (658.03)	1282.27 (495.09)	-0.40 (0.12)
Reduced activity	14.19 (0.53)	6.5 (0.8)	21.88 (0.79)	1.53 (0.29)	1688.58 (322.48)	2529.92 (450.64)	628.59 (227.38)	-0.42 (0.14)
Early activity	12.97 (0.55)	5.54 (0.79)	20.4 (0.73)	1.73 (0.23)	2237.79 (368.08)	3839.14 (703.04)	1163.29 (511.24)	-0.36 (0.13)
Late activity	15.66 (0.65)	7.88 (0.85)	23.44 (0.85)	1.75 (0.18)	2213.97 (304.36)	3868.43 (642.66)	1173.9 (411.5)	-0.44 (0.14)
Early activity with short active period	12.99 (0.65)	7.08 (0.83)	18.89 (1.16)	1.65 (0.26)	2606.41 (609.99)	4290.21 (1241.03)	1200.96 (501.88)	0.07 (0.29)
Late rising with short active period	14.66 (0.72)	8.83 (1.15)	20.49 (1.12)	1.68 (0.33)	2511.47 (760.59)	4275.28 (1738.7)	1003.51 (515.46)	0.13 (0.34)
Early, dampened rhythm with short active period	12.71 (0.95)	6.82 (1.21)	18.6 (1.54)	1.22 (0.25)	1917.22 (398.34)	2296.71 (466.29)	576.59 (223.78)	0.03 (0.25)
Late with reduced activity	15.99 (1.16)	8.3 (1.47)	23.68 (1.23)	1.46 (0.30)	1682.3 (315.54)	2429.83 (537.53)	584.5 (216.95)	-0.41 (0.20)

Table 10. Pearson correlations of CAR parameters

	Amplitude	Mesor	St. amplitude	Pseudo F	Up-mesor	Acrophase	Down-mesor	Alpha
Amplitude	-	0.81	-0.16	0.56	0.05	-0.05	-0.10	0.26
Mesor	0.81	-	-0.41	0.44	0.11	-0.14	-0.26	0.43
St. amplitude	-0.16	-0.41	-	0.26	-0.31	0.31	0.62	-0.16
Pseudo F	0.56	0.44	0.26	-	-0.07	-0.04	-0.004*	-0.08
Up-mesor	0.05	0.11	-0.31	-0.07	-	0.68	0.20	0.43
Acrophase	-0.05	-0.14	-0.04	0.68	0.68	-	0.86	-0.31
Down-mesor	-0.10	-0.26	-0.004	-0.004*	0.20	0.86	-	-0.71
Alpha	0.26	0.43	-0.16	-0.08	0.43	-0.31	-0.71	-

St. = standardized; all p values <0.05 unless noted with a *

Table 11. Latent classes of community-dwelling older men based on circadian rest-activity rhythm (CAR) indicators (n=3001)

Group Name	Probable Characteristics	Prevalence (%)
Normal rhythm	All parameters normative	32.09
Reduced activity	Low height measures	10.06
Early activity	Early up-mesor/peak	10.53
Late activity	Late peak/down-mesor	14.46
Early activity with short active period	Early peak/down-mesor w/ high alpha	9.63
Late rising with short active period	Late up-mesor w/ high alpha	8.23
Early, dampened rhythm with short active period	Early peak/down-mesor, low st. amp and height, high alpha	6.80
Late with reduced activity	Late peak/down-mesor with low height measures	8.20

Note: Prevalence in entire sample shown; prevalence for final subset with complete covariate data shown elsewhere

Table 12. Age and site adjusted odds of membership in LCA-derived CAR subgroups (vs. normal CAR, 32.18%)

	Altered height	Altered timing		Altered timing and active period		Altered timing and height	
	Reduced activity (9.79%)	Early activity (10.70%)	Late activity (14.36%)	Early activity with short active period (10.54%)	Late rising with short active period (8.27%)	Early, dampened rhythm with short active period (6.48%)	Late with reduced activity (7.68%)
Age (per SD)	1.60 (1.41-1.82)	0.95 (0.82-1.09)	0.94 (0.83-1.06)	1.05 (0.92-1.21)	1.12 (0.97-1.30)	1.43 (1.23-1.66)	1.52 (1.32-1.75)
Study Site (vs. PI):							
BI	1.18 (0.74-1.89)	2.35 (1.41-3.92)	0.33 (0.22-0.50)	1.02 (0.66-1.60)	0.47 (0.28-0.77)	0.92 (0.56-1.52)	0.66 (0.41-1.07)
MN	1.03 (0.65-1.63)	1.72 (1.02-2.90)	0.49 (0.33-0.71)	0.91 (0.58-1.41)	0.55 (0.35-0.87)	0.49 (0.28-0.84)	0.61 (0.38-0.96)
PA	0.74 (0.46-1.21)	1.57 (0.91-2.71)	0.75 (0.52-1.07)	0.75 (0.47-1.20)	0.64 (0.40-1.01)	0.55 (0.32-0.94)	0.64 (0.40-1.01)
PO	1.15 (0.73-1.82)	1.50 (0.87-2.57)	0.46 (0.31-0.68)	0.53 (0.32-0.87)	0.43 (0.26-0.71)	0.45 (0.25-0.79)	0.41 (0.25-0.68)
SD	0.86 (0.54-1.38)	2.13 (1.29-3.54)	0.40 (0.27-0.59)	0.76 (0.48-1.19)	0.57 (0.36-0.89)	0.93 (0.58-1.49)	0.47 (0.29-0.76)
Race:							
Black vs. White	1.04 (0.46-2.32)	1.14 (0.57-2.29)	1.92 (1.06-3.47)	1.37 (0.68-2.76)	2.50 (1.28-4.90)	1.42 (0.60-3.35)	1.96 (0.95-4.05)
Other vs. White	1.50 (0.86-2.61)	1.05 (0.60-1.83)	1.31 (0.82-2.11)	1.13 (0.62-2.04)	1.77 (1.02-3.07)	1.02 (0.50-2.08)	1.59 (0.88-2.87)
Alcohol use per week:							
1-13 drinks vs. <1 drink	0.93 (0.71-1.23)	0.81 (0.62-1.06)	0.94 (0.74-1.2)	0.94 (0.71-1.25)	0.83 (0.62-1.13)	0.73 (0.53-1.02)	0.73 (0.55-0.99)
14+ drinks vs. <1 drink	0.78 (0.41-1.50)	1.12 (0.66-1.92)	0.86 (0.50-1.48)	1.45 (0.85-2.5)	1.51 (0.87-2.62)	1.10 (0.58-2.09)	0.33 (0.13-0.85)
Daily caffeine intake (per SD)	0.97 (0.84-1.11)	1.10 (0.98-1.24)	0.97 (0.86-1.08)	1.02 (0.90-1.17)	0.94 (0.81-1.09)	0.81 (0.68-0.97)	0.94 (0.81-1.09)
Education:							
Less than high school vs. College/graduate school	1.3 (0.73-2.31)	1.35 (0.72-2.52)	0.54 (0.28-1.05)	1.84 (1.05-3.25)	1.88 (1.05-3.38)	1.23 (0.61-2.51)	1.63 (0.92-2.91)
High school diploma vs. College/graduate school	0.62 (0.40-0.94)	1.10 (0.75-1.59)	0.57 (0.40-0.82)	1.26 (0.87-1.81)	1.1 (0.74-1.63)	1.26 (0.83-1.91)	0.77 (0.50-1.17)
Smoking Status:							
Former vs. None	1.07 (0.82-1.40)	0.98 (0.75-1.28)	0.81 (0.64-1.02)	1.23 (0.93-1.62)	1.25 (0.93-1.68)	1.25 (0.91-1.72)	1.20 (0.89-1.61)
Current vs. None	1.59 (0.41-6.15)	2.70 (0.95-7.62)	2.87 (1.14-7.20)	4.45 (1.66-1.88)	2.97 (0.94-9.36)	2.48 (0.64-9.64)	7.83 (3.02-0.32)

Table 12 continued

BMI (per SD)	1.39 (1.21-1.59)	1.12 (0.97-1.28)	1.07 (0.94-1.21)	1.22 (1.06-1.41)	1.42 (1.23-1.64)	1.82 (1.57-2.11)	1.47 (1.27-1.70)
Physical Activity (per SD)	0.60 (0.51-0.70)	1.12 (0.99-1.26)	0.80 (0.71-0.90)	0.96 (0.84-1.09)	0.81 (0.70-0.94)	0.61 (0.51-0.73)	0.44 (0.37-0.52)
Cognitive function (per SD)	0.87 (0.76-0.99)	0.94 (0.81-1.08)	1.05 (0.91-1.20)	0.89 (0.77-1.02)	0.76 (0.67-0.87)	0.75 (0.66-0.87)	0.88 (0.76-1.02)
Anxiety symptoms (per SD)	1.10 (0.97-1.26)	0.98 (0.85-1.13)	1.00 (0.88-1.13)	1.08 (0.95-1.24)	1.27 (1.12-1.44)	0.90 (0.76-1.08)	1.29 (1.13-1.46)
Depressive symptoms (per SD)	1.41 (1.24-1.60)	1.07 (0.93-1.25)	1.10 (0.96-1.25)	1.06 (0.91-1.24)	1.39 (1.21-1.59)	1.31 (1.13-1.52)	1.60 (1.41-1.81)
Worse global sleep quality (per SD)	1.24 (1.09-1.41)	1.03 (0.90-1.18)	1.08 (0.96-1.22)	1.12 (0.98-1.29)	1.39 (1.21-1.59)	1.24 (1.06-1.44)	1.42 (1.24-1.62)
Daytime sleepiness (per SD)	1.07 (0.94-1.22)	0.98 (0.86-1.12)	1.01 (0.90-1.13)	0.98 (0.86-1.12)	0.95 (0.83-1.10)	1.10 (0.94-1.27)	1.16 (1.01-1.34)
Chronic Disease History							
IADL impairment (per additional)	1.72 (1.45-2.04)	1.37 (1.12-1.67)	1.40 (1.17-1.68)	1.16 (0.93-1.45)	1.9 (1.60-2.27)	1.80 (1.49-2.17)	2.22 (1.88-2.62)
Fall in past 12 months	1.34 (1.01-1.77)	1.03 (0.77-1.37)	1.37 (1.07-1.75)	0.94 (0.69-1.27)	1.54 (1.15-2.08)	1.16 (0.83-1.62)	1.64 (1.22-2.21)
Peripheral vascular disease	1.38 (0.91-2.10)	0.82 (0.49-1.35)	1.11 (0.74-1.67)	1.44 (0.93-2.21)	1.51 (0.96-2.36)	1.27 (0.77-2.09)	1.65 (1.07-2.54)
Osteoarthritis	1.14 (0.84-1.55)	1.01 (0.75-1.37)	1.08 (0.83-1.42)	0.79 (0.57-1.10)	1.41 (1.03-1.93)	1.09 (0.76-1.56)	1.39 (1.01-1.91)
Rheumatoid Arthritis	1.18 (0.71-1.95)	1.08 (0.64-1.80)	1.60 (1.05-2.43)	1.28 (0.78-2.12)	1.61 (0.98-2.65)	1.65 (0.97-2.78)	2.17 (1.37-3.44)
Hypertension	1.25 (0.96-1.62)	1.12 (0.87-1.44)	1.03 (0.82-1.29)	1.35 (1.04-1.76)	1.56 (1.18-2.07)	2.23 (1.62-3.06)	1.53 (1.15-2.04)
Stroke	1.15 (0.54-2.45)	1.55 (0.78-3.09)	1.19 (0.59-2.39)	1.18 (0.54-2.57)	2.74 (1.43-5.24)	1.84 (0.86-3.93)	2.31 (1.19-4.49)
Angina	1.35 (0.95-1.93)	1.27 (0.89-1.82)	1.10 (0.79-1.54)	0.99 (0.67-1.47)	1.58 (1.09-2.29)	1.49 (1.00-2.23)	1.53 (1.06-2.22)
Congestive Heart Failure	2.27 (1.36-3.80)	1.34 (0.73-2.44)	1.15 (0.65-2.02)	1.70 (0.96-3.01)	1.55 (0.83-2.87)	2.38 (1.33-4.25)	2.71 (1.60-4.59)
Myocardial Infarction	1.16 (0.83-1.61)	0.95 (0.66-1.35)	0.64 (0.45-0.91)	0.89 (0.62-1.29)	1.76 (1.26-2.46)	1.11 (0.75-1.64)	1.42 (1.01-2.01)
Diabetes	1.60 (1.11-2.30)	0.75 (0.48-1.16)	1.05 (0.74-1.48)	1.14 (0.77-1.69)	1.37 (0.92-2.04)	1.73 (1.15-2.61)	1.70 (1.16-2.51)
COPD	2.78 (1.63-4.75)	1.92 (1.08-3.42)	1.37 (0.78-2.42)	1.05 (0.52-2.11)	1.84 (0.99-3.42)	1.75 (0.90-3.40)	1.95 (1.06-3.60)
Parkinson's	3.40 (1.17-9.88)	undefined	0.70 (0.14-3.38)	undefined	3.13 (0.98-10.01)	5.33 (1.82-5.56)	5.05 (1.79-4.27)
Renal disease	5.30 (1.30-1.50)	4.05 (0.90-8.28)	4.26 (1.01-8.00)	2.22 (0.37-3.41)	8.18 (2.02-33.14)	5.73 (1.26-6.03)	3.5 (0.70-7.64)
Cataracts	1.17 (0.90-1.54)	0.96 (0.74-1.26)	1.06 (0.84-1.35)	1.15 (0.88-1.52)	1.17 (0.87-1.56)	1.30 (0.95-1.79)	1.15 (0.86-1.54)
Liver disease	0.34 (0.08-1.47)	0.82 (0.33-2.05)	1.20 (0.58-2.46)	1.44 (0.65-3.18)	0.55 (0.16-1.87)	0.74 (0.22-2.51)	0.62 (0.18-2.10)
Severe SDB (AHI $\geq$ 30)	1.65 (1.17-2.33)	0.86 (0.58-1.29)	1.11 (0.80-1.55)	1.16 (0.80-1.68)	1.40 (0.97-2.04)	1.75 (1.19-2.56)	1.86 (1.3-2.67)

Table 12 continued

Medication Use							
Antidepressant use	1.54 (0.93-2.56)	1.21 (0.71-2.04)	1.93 (1.26-2.97)	1.08 (0.61-1.90)	1.79 (1.06-3.01)	1.85 (1.06-3.21)	3.64 (2.33-5.68)
Non-benzodiazepine non-barbiturate sedatives/hypnotics	1.17 (0.5-2.72)	0.85 (0.34-2.15)	1.41 (0.66-2.99)	0.16 (0.02-1.21)	0.63 (0.19-2.16)	0.91 (0.31-2.72)	1.37 (0.56-3.31)
Benzodiazepines use	1.19 (0.60-2.36)	0.87 (0.42-1.81)	1.80 (1.03-3.14)	0.78 (0.35-1.71)	2.25 (1.22-4.15)	1.38 (0.66-2.88)	2.90 (1.63-5.15)
Current NSAID use	1.03 (0.74-1.43)	1.13 (0.82-1.54)	0.96 (0.72-1.28)	0.93 (0.67-1.30)	0.99 (0.70-1.41)	0.64 (0.42-0.98)	1.01 (0.71-1.44)
Current corticosteroid use (oral/nasal/inhaled)	1.62 (1.07-2.46)	0.99 (0.62-1.58)	1.36 (0.93-2.00)	0.94 (0.57-1.54)	0.99 (0.59-1.66)	1.06 (0.61-1.84)	1.81 (1.17-2.81)
Inflammatory Markers							
log(IL-6 + 1)	1.82 (1.33-2.48)	1.16 (0.81-1.67)	1.42 (1.04-1.92)	1.36 (0.96-1.92)	1.76 (1.26-2.46)	2.33 (1.69-3.20)	2.15 (1.58-2.93)
log(CRP + 1)	1.64 (1.31-2.04)	1.32 (1.05-1.64)	1.31 (1.07-1.61)	1.50 (1.20-1.87)	1.57 (1.24-1.99)	1.77 (1.38-2.28)	1.96 (1.56-2.47)
log(TNF-α + 1)	1.90 (1.11-3.25)	2.13 (1.28-3.56)	1.98 (1.24-3.16)	1.60 (0.93-2.74)	1.39 (0.78-2.49)	2.01 (1.06-3.78)	2.39 (1.35-4.25)
log(TNF-αsRII + 1)	2.81 (1.85-4.26)	1.81 (1.20-2.73)	1.74 (1.19-2.53)	1.63 (1.07-2.50)	2.23 (1.42-3.50)	2.17 (1.33-3.55)	2.49 (1.58-3.92)
log(IFN-γ + 1)	1.10 (0.87-1.40)	1.05 (0.84-1.33)	1.17 (0.95-1.44)	0.93 (0.72-1.19)	1.10 (0.85-1.42)	0.97 (0.72-1.29)	1.16 (0.90-1.50)

*Crude associations adjusted for age and study site

Table 13. Final model (n=2514) showing adjusted odds (95% confidence interval) of membership in LCA-derived CAR subgroups (vs. normal CAR, 32.18%)

	Altered height	Altered timing		Altered timing and active period		Altered timing and height	
	Reduced activity (9.79%)	Early activity (10.70%)	Late activity (14.36%)	Early activity with short active period (10.54%)	Late rising with short active period (8.27%)	Early, dampened rhythm with short active period (6.48%)	Late with reduced activity (7.68%)
Age (per SD)	1.39 (1.17-1.66)	0.92 (0.77-1.09)	0.88 (0.76-1.03)	1.07 (0.90-1.26)	1.00 (0.82-1.23)	1.37 (1.12-1.68)	1.17 (0.97-1.42)
Alcohol use per week:							
1-13 drinks vs. <1 drink	0.84 (0.60-1.17)	0.83 (0.61-1.14)	0.94 (0.71-1.24)	1.03 (0.75-1.41)	0.84 (0.57-1.24)	0.60 (0.47-1.03)	0.72 (0.50-1.03)
14+ drinks vs. <1 drink	0.68 (0.28-1.62)	1.52 (0.81-2.85)	1.25 (0.67-2.31)	1.93 (1.03-3.59)	2.38 (1.19-4.75)	1.01 (0.42-2.42)	0.21 (0.05-0.93)
Education:							
Less than high school vs. College/graduate school	0.73 (0.35-1.51)	1.12 (0.53-2.37)	0.33 (0.15-0.75)	1.31 (0.68-2.53)	1.23 (0.60-2.53)	0.73 (0.33-1.62)	0.71 (0.32-1.57)
High school diploma vs. College/graduate school	0.57 (0.35-0.95)	1.20 (0.78-1.84)	0.49 (0.32-0.74)	1.18 (0.79-1.78)	0.74 (0.44-1.25)	0.92 (0.55-1.51)	0.61 (0.36-1.02)
Smoking Status:							
Former vs. None	0.92 (0.66-1.28)	0.99 (0.72-1.34)	0.76 (0.58-1.00)	1.20 (0.88-1.63)	1.09 (0.75-1.59)	1.11 (0.76-1.62)	1.21 (0.84-1.75)
Current vs. None	0.93 (0.15-5.78)	2.35 (0.74-7.49)	2.59 (0.92-7.29)	3.76 (1.3-10.87)	1.41 (0.28-7.19)	2.02 (0.38-10.4)	5.12 (1.49-17.56)
BMI (per SD)	1.31 (1.10-1.56)	0.98 (0.82-1.16)	1.06 (0.91-1.23)	1.13 (0.96-1.33)	1.29 (1.06-1.56)	1.69 (1.40-2.03)	1.27 (1.05-1.53)
Physical Activity (per SD)	0.57 (0.47-0.69)	1.18 (1.02-1.37)	0.79 (0.68-0.91)	0.99 (0.85-1.16)	0.89 (0.74-1.07)	0.66 (0.53-0.81)	0.50 (0.40-0.62)
Cognitive function (per SD)	0.88 (0.74-1.04)	1.01 (0.85-1.20)	1.01 (0.86-1.19)	0.95 (0.80-1.12)	0.80 (0.67-0.95)	0.81 (0.68-0.97)	1.01 (0.83-1.22)
Anxiety symptoms (per SD)	0.95 (0.80-1.12)	0.95 (0.80-1.11)	0.95 (0.82-1.10)	1.06 (0.91-1.22)	1.15 (0.99-1.35)	0.83 (0.68-1.02)	1.12 (0.96-1.31)
Chronic Disease History							
IADL impairment (per additional)	1.59 (1.26-1.99)	1.49 (1.16-1.91)	1.35 (1.07-1.70)	1.01 (0.77-1.34)	1.79 (1.41-2.28)	1.40 (1.09-1.81)	1.94 (1.56-2.40)

Table 13 continued

Hypertension	0.93 (0.68-1.29)	1.09 (0.80-1.47)	0.98 (0.74-1.28)	1.26 (0.94-1.70)	1.30 (0.90-1.88)	1.66 (1.14-2.43)	1.10 (0.77-1.57)
CHF	2.03 (1.07-3.85)	1.45 (0.72-2.92)	1.12 (0.55-2.29)	1.52 (0.79-2.91)	0.69 (0.27-1.80)	1.63 (0.76-3.44)	1.41 (0.67-2.95)
Myocardial Infarction	0.96 (0.63-1.46)	0.86 (0.57-1.30)	0.62 (0.42-0.93)	0.85 (0.57-1.28)	1.69 (1.11-2.58)	0.82 (0.51-1.34)	1.02 (0.66-1.58)
COPD	2.47 (1.30-4.70)	1.56 (0.78-3.10)	1.42 (0.75-2.72)	0.74 (0.33-1.64)	1.31 (0.60-2.84)	1.39 (0.62-3.10)	1.29 (0.60-2.78)
Inflammatory Markers							
log(CRP + 1)	1.47 (1.13-1.90)	1.17 (0.91-1.51)	1.21 (0.96-1.51)	1.38 (1.09-1.75)	1.42 (1.07-1.88)	1.47 (1.10-1.96)	1.61 (1.23-2.10)
log(TNF-α + 1)	1.22 (0.66-2.26)	1.86 (1.07-3.26)	1.79 (1.08-2.95)	1.25 (0.70-2.20)	0.82 (0.40-1.66)	1.22 (0.60-2.48)	1.48 (0.77-2.84)

Estimates also adjusted for study site

Table 14. The item pool selected from to achieve the final depression LCA

	GDS only	GDS reduced	GDAS only	Combined Depression
Geriatric Depression Scale (GDS)				
Are you basically satisfied with your life?	x			
Have you dropped many of your activities and interests?	x	x		x
Do you feel that your life is empty?	x	x		x
Do you often get bored?	x			
Are you in good spirits most of the time?	x	x		
Are you afraid that something bad is going to happen to you?	x			
Do you feel happy most of the time?	x			
Do you often feel helpless?	x	x		x
Do you prefer to stay at home, rather than going out and doing new things?	x	x		x
Do you feel you have more problems with memory than most?	x	x		x
Do you think it is wonderful to be alive now?	x			
Do you feel pretty worthless the way you are now?	x	x		x
Do you feel full of energy?	x	x		
Do you feel that your situation is hopeless?	x	x		
Do you think that most people are better off than you are?	x			
Goldberg Depression and Anxiety Scale (GDAS)				
Have you been lacking in energy?			x	x
Have you lost interest in things?			x	x
Have you lost confidence in yourself?			x	x
Have you felt hopeless?			x	x
Have you had difficulty concentrating?			x	x
Have you lost weight (due to poor appetite)?			x	x
Have you been waking early?				
Have you felt slowed up?			x	x
Have you tended to feel worse in the morning?			x	x
Have you felt keyed up or on edge?				
Have you been worrying a lot?				
Have you been irritable?			x	x
Have you had difficulty relaxing?				
Have you been sleeping poorly?				
Have you had headaches or neckaches?				
Have you had any of the following: trembling, tingling, dizzy spells, sweating, diarrhoea, or needing to pass water more often than usual?				
Have you been worrying about your health?				

Table 14 continued

Have you had difficulty falling asleep?	
Additional Depression Items	
How much of the time during the past 4 weeks have you felt downhearted and blue? (A good bit of the time/most of the time/all of the time vs. some of the time/a little of the time/none of the time)	x
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities because of any emotional problems (such as feeling depressed or anxious)	
... Accomplished less than you would like?	x
… Didn't do work or other activities as carefully as usual?	x

Table 15. BIC for different number of latent classes using all depression indicators

Number of latent classes	Log likelihood	BIC	Entropy
1	-19814.24	12503.40	1.00
2	-16944.18	6915.41	0.86
3	-16274.09	5727.36	0.83
4	-16141.24	5613.80	0.85
5	**-16059.53**	**5602.52**	**0.83**
6	-15999.99	5635.57	0.85

BOLD solution selected

Table 16. Descriptive mood characteristics of depression latent classes

Name of latent class	Mean GDS (SD)	Mean GAS (SD)	Percent with impairment*
Not depressed	0.62 (0.81)	0.32 (0.91)	1.37 (22)
Probable somatic/apathy	2.18 (1.30)	1.00 (1.78)	2.03 (17)
Probable somatic/apathy with impairment	2.25 (1.56)	1.78 (2.20)	100 (215)
Apathy/somatic with probable impairment	4.23 (1.78)	3.00 (2.73)	63.68 (128)
Depressed	8.40 (2.38)	4.40 (2.74)	87.23 (123)

***** Accomplished less than you would like due to emotional issue at least "a good bit of the time" over the past two weeks

Table 17. Age and site adjusted odds of membership in LCA-derived depression subgroups (vs. non-depressed, 53.86%)

	Depressed (4.25%)	Apathy/somatic w/ probable impairment (8.45%)	Probable somatic/apathy w/ impairment (5.74%)	Probable somatic/apathy (27.70%)
Age (per SD)	1.55 (1.30-1.84)	1.63 (1.4-1.89)	1.45 (1.25-1.67)	1.53 (1.41-1.68)
Study Site (vs. PI):				
BI	0.73 (0.41-1.30)	1.58 (1.00-2.51)	0.99 (0.61-1.63)	0.93 (0.70-1.25)
MN	0.52 (0.29-0.91)	0.54 (0.32-0.91)	0.55 (0.33-0.93)	0.61 (0.46-0.81)
PA	0.37 (0.20-0.69)	0.48 (0.28-0.82)	0.85 (0.53-1.37)	0.58 (0.43-0.77)
PO	0.66 (0.38-1.16)	0.87 (0.53-1.43)	0.93 (0.57-1.51)	0.54 (0.40-0.74)
SD	0.62 (0.36-1.07)	0.43 (0.24-0.75)	0.64 (0.39-1.06)	0.69 (0.52-0.91)
Race:				
Black vs. White	1.84 (0.81-4.21)	1.99 (1.04-3.80)	1.26 (0.58-2.72)	1.25 (0.79-1.99)
Other vs. White	0.99 (0.44-2.23)	1.37 (0.71-2.61)	1.03 (0.57-1.88)	1.01 (0.70-1.47)
Alcohol use per week:				
1-13 drinks vs. <1 drink	0.91 (0.63-1.32)	0.62 (0.45-0.85)	0.74 (0.54-1.00)	0.77 (0.64-0.92)
14+ drinks vs. <1 drink	0.86 (0.40-1.87)	0.57 (0.28-1.17)	0.60 (0.30-1.19)	0.64 (0.43-0.95)
Daily caffeine intake (per SD)	0.91 (0.75-1.10)	0.96 (0.82-1.13)	1.11 (0.96-1.27)	1.01 (0.93-1.11)
Education:				
Less than high school vs. College/graduate school	2.77 (1.50-5.12)	1.56 (0.82-2.97)	1.67 (0.89-3.11)	1.75 (1.18-2.58)
High school diploma vs. College/graduate school	1.08 (0.65-1.79)	1.51 (1.02-2.25)	1.12 (0.73-1.71)	1.23 (0.96-1.57)
Smoking Status:				
Former vs. None	1.39 (0.96-2.01)	1.5 (1.09-2.06)	1.02 (0.76-1.37)	1.18 (0.99-1.41)
Current vs. None	4.15 (1.70-10.15)	1.69 (0.57-5.03)	1.55 (0.58-4.14)	1.14 (0.58-2.24)
BMI (per SD)	1.16 (0.97-1.38)	1.19 (1.03-1.39)	1.28 (1.11-1.48)	1.20 (1.10-1.32)
Physical Activity (per SD)	0.45 (0.37-0.56)	0.6 (0.50-0.71)	0.79 (0.68-0.92)	0.72 (0.66-0.79)
Cognitive function (per SD)	0.67 (0.58-0.77)	0.79 (0.68-0.90)	0.9 (0.77-1.05)	0.85 (0.77-0.93)
Anxiety symptoms (per SD)	6.86 (5.69-8.28)	4.74 (4.01-5.62)	3.38 (2.85-4.00)	2.38 (2.06-2.75)
Worse global sleep quality (per SD)	3.59 (3.04-4.25)	2.99 (2.58-3.48)	2.36 (2.03-2.74)	1.97 (1.78-2.18)
Daytime sleepiness (per SD)	1.87 (1.59-2.21)	2.11 (1.83-2.43)	1.25 (1.08-1.45)	1.39 (1.27-1.52)

Table 17 continued

WASO ≥ 90 minutes	1.28 (0.88-1.85)	2.08 (1.54-2.82)	1.66 (1.23-2.24)	1.48 (1.23-1.77)
SL ≥ 60 minutes	2.54 (1.59-4.05)	2.60 (1.72-3.92)	1.47 (0.92-2.34)	1.54 (1.16-2.05)
Sleep duration				
<5 vs. 5-8 hours	1.43 (0.86-2.38)	2.18 (1.47-3.25)	1.34 (0.86-2.10)	1.62 (1.25-2.09)
>8 vs. 5-8 hours	1.08 (0.56-2.09)	1.11 (0.64-1.95)	1.11 (0.65-1.88)	0.91 (0.65-1.28)
Circadian Activity Rhythms				
Low amplitude (Q1 vs. Q2-4)	2.22 (1.53-3.23)	2.40 (1.75-3.31)	1.52 (1.09-2.11)	1.92 (1.57-2.34)
Low mesor (Q1 vs. Q2-4)	2.17 (1.50-3.15)	1.76 (1.27-2.44)	1.28 (0.92-1.79)	1.62 (1.33-1.97)
Low st. amplitude (Q1 vs. Q2-4)	1.36 (0.93-2.00)	1.23 (0.88-1.72)	1.21 (0.87-1.68)	1.29 (1.06-1.57)
Low psuedo-F (Q1 vs. Q2-4)	2.83 (1.96-4.07)	2.31 (1.68-3.20)	1.88 (1.37-2.60)	1.70 (1.39-2.08)
Acrophase				
Early (Q1 vs. Q2/3)	0.81 (0.51-1.30)	0.66 (0.45-0.98)	0.77 (0.53-1.12)	0.84 (0.68-1.03)
Late (Q4 vs. Q2/3)	2.12 (1.43-3.14)	1.53 (1.08-2.16)	1.59 (1.13-2.22)	1.21 (0.98-1.50)
Up-mesor				
Early (Q1 vs. Q2/3)	0.71 (0.44-1.14)	0.81 (0.56-1.19)	0.86 (0.59-1.24)	0.75 (0.61-0.93)
Late (Q4 vs. Q2/3)	1.81 (1.21-2.68)	1.60 (1.12-2.27)	1.75 (1.25-2.45)	1.25 (1.02-1.55)
Down-mesor				
Early (Q1 vs. Q2/3)	1.23 (0.79-1.92)	0.66 (0.44-0.98)	1.00 (0.70-1.43)	0.99 (0.81-1.22)
Late (Q4 vs. Q2/3)	2.06 (1.37-3.09)	1.16 (0.81-1.65)	1.36 (0.97-1.92)	1.16 (0.94-1.43)
Chronic Disease History				
IADL impairment (per additional)	3.21 (2.69-3.84)	2.75 (2.32-3.26)	2.09 (1.73-2.53)	2.12 (1.84-2.44)
Fall in past 12 months	3.64 (2.56-5.19)	2.51 (1.85-3.41)	1.50 (1.10-2.04)	1.71 (1.42-2.06)
Peripheral vascular disease	2.43 (1.47-4.01)	2.88 (1.88-4.40)	2.55 (1.66-3.91)	1.91 (1.43-2.56)
Osteoarthritis	3.23 (2.25-4.65)	2.83 (2.06-3.89)	1.88 (1.36-2.60)	1.60 (1.31-1.97)
Rheumatoid Arthritis	3.63 (2.23-5.92)	2.97 (1.90-4.65)	1.38 (0.79-2.41)	1.98 (1.44-2.72)
Hypertension	1.50 (1.06-2.13)	1.62 (1.20-2.19)	1.01 (0.76-1.34)	1.45 (1.22-1.73)
Stroke	3.62 (1.73-7.59)	3.24 (1.68-6.24)	2.72 (1.37-5.38)	2.34 (1.46-3.77)
Angina	2.49 (1.65-3.74)	2.06 (1.43-2.97)	1.45 (0.99-2.14)	1.51 (1.19-1.92)
Congestive Heart Failure	2.29 (1.26-4.14)	2.48 (1.49-4.14)	1.78 (1.02-3.10)	1.36 (0.94-1.97)
Myocardial Infarction	1.75 (1.15-2.66)	1.72 (1.20-2.47)	1.16 (0.78-1.71)	1.64 (1.31-2.05)
Diabetes	1.69 (1.06-2.68)	1.39 (0.91-2.12)	1.16 (0.75-1.79)	1.56 (1.22-1.99)
COPD	4.17 (2.35-7.43)	2.67 (1.51-4.72)	1.59 (0.81-3.11)	2.19 (1.48-3.24)
Parkinson's	9.03 (2.49-2.76)	11.95 (4.02-5.62)	6.43 (1.92-1.47)	4.55 (1.71-2.15)

Table 17 continued

Renal disease	2.67 (0.73-9.81)	1.15 (0.25-5.32)	1.78 (0.49-6.50)	2.11 (0.94-4.74)
Cataracts	1.79 (1.24-2.57)	1.32 (0.97-1.79)	1.02 (0.76-1.37)	1.39 (1.17-1.66)
Liver disease	1.80 (0.62-5.22)	0.61 (0.14-2.59)	1.88 (0.81-4.35)	1.17 (0.63-2.16)
Severe SDB (AHI ≥ 30)	1.61 (1.03-2.52)	1.68 (1.14-2.47)	1.54 (1.06-2.25)	1.55 (1.23-1.95)
Medication Use				
Antidepressant use	7.49 (4.72-1.88)	4.76 (3.05-7.44)	3.37 (2.10-5.42)	2.09 (1.47-2.96)
Non-benzodiazepine non-barbiturate sedatives /hypnotics	2.91 (0.95-8.85)	4.87 (2.20-0.78)	3.01 (1.22-7.40)	2.41 (1.25-4.64)
Benzodiazepines use	4.03 (2.17-7.51)	3.36 (1.92-5.91)	2.57 (1.39-4.72)	1.55 (0.99-2.43)
Current NSAID use	1.72 (1.15-2.57)	1.76 (1.25-2.47)	1.11 (0.77-1.60)	1.21 (0.97-1.50)
Current corticosteroid use (oral/nasal/inhaled)	2.14 (1.29-3.53)	1.21 (0.72-2.04)	1.38 (0.86-2.21)	1.41 (1.06-1.89)
Inflammatory Markers				
log(IL-6 + 1)	1.56 (1.08-2.24)	1.63 (1.20-2.22)	1.59 (1.17-2.15)	1.28 (1.04-1.57)
log(CRP + 1)	1.54 (1.16-2.03)	1.24 (0.97-1.60)	1.44 (1.14-1.82)	1.24 (1.07-1.43)
log(TNF-α + 1)	1.94 (0.96-3.93)	1.48 (0.80-2.74)	1.09 (0.60-1.99)	1.43 (1.01-2.02)
log(TNF-αsRII + 1)	2.49 (1.44-4.33)	1.62 (1.00-2.62)	1.42 (0.88-2.28)	2.16 (1.64-2.84)
log(IFN-γ + 1)	0.85 (0.60-1.20)	0.99 (0.75-1.32)	1.20 (0.94-1.55)	0.95 (0.81-1.11)

*Crude associations adjusted for age and study site

Table 18. Final model (n=2473) showing adjusted odds (95% confidence interval) of membership in LCA-derived depression subgroups (vs. non-depressed reference group, 53.86%)

	Depressed (4.25%)	Apathy/somatic w/ probable impairment (8.45%)	Probable somatic/apathy w/ impairment (5.74%)	Probable somatic/apathy (27.70%)
Age (per SD)	1.08 (0.97-1.20)	1.18 (1.10-1.27)	1.08 (0.97-1.20)	1.14 (1.09-1.19)
Physical Activity (per SD)	0.77 (0.69-0.86)	0.91 (0.85-0.98)	0.99 (0.92-1.08)	0.94 (0.90-0.98)
Anxiety symptoms (per SD)	2.13 (1.97-2.30)	1.56 (1.47-1.66)	1.32 (1.22-1.42)	1.10 (1.05-1.15)
Worse global sleep quality (per SD)	1.18 (1.07-1.30)	1.31 (1.22-1.40)	1.21 (1.11-1.31)	1.22 (1.17-1.27)
Daytime sleepiness (per SD)	1.16 (1.06-1.28)	1.30 (1.22-1.39)	1.04 (0.96-1.12)	1.10 (1.06-1.15)
Circadian Activity Rhythms				
Low amplitude (Q1 vs. Q2-4)	1.16 (0.92-1.44)	1.32 (1.13-1.53)	1.14 (0.95-1.37)	1.19 (1.08-1.31)
Up-mesor				
Early (Q1 vs. Q2/3)	0.92 (0.72-1.18)	0.82 (0.69-0.96)	0.92 (0.77-1.11)	0.88 (0.80-0.97)
Late (Q4 vs. Q2/3)	0.93 (0.74-1.18)	0.99 (0.85-1.17)	1.18 (0.98-1.42)	0.96 (0.87-1.06)
Down-mesor				
Early (Q1 vs. Q2/3)	1.25 (0.99-1.59)	0.76 (0.65-0.90)	0.92 (0.77-1.11)	0.94 (0.86-1.04)
Late (Q4 vs. Q2/3)	1.46 (1.15-1.84)	0.94 (0.79-1.11)	1.08 (0.90-1.30)	1.01 (0.91-1.11)
Chronic Disease History				
IADL impairment (per additional)	1.12 (1.00-1.24)	1.12 (1.03-1.21)	1.05 (0.95-1.16)	1.09 (1.04-1.16)
Fall in past 12 months	1.33 (1.09-1.63)	1.18 (1.02-1.35)	1.06 (0.90-1.25)	1.12 (1.03-1.22)
Peripheral vascular disease	1.07 (0.80-1.43)	1.36 (1.11-1.65)	1.39 (1.10-1.76)	1.18 (1.04-1.35)
Rheumatoid Arthritis	1.48 (1.12-1.97)	1.28 (1.03-1.60)	0.82 (0.60-1.11)	1.13 (0.98-1.31)
Stroke	1.57 (1.03-2.39)	1.30 (0.95-1.78)	1.11 (0.74-1.65)	1.28 (1.04-1.57)
COPD	1.57 (1.11-2.21)	0.95 (0.71-1.27)	1.06 (0.75-1.48)	1.25 (1.05-1.48)
Cataracts	1.06 (0.87-1.29)	0.93 (0.81-1.06)	0.86 (0.73-1.00)	1.07 (0.99-1.16)
Inflammatory Markers				
log(CRP + 1)	1.10 (0.95-1.27)	1.01 (0.91-1.12)	1.16 (1.03-1.31)	0.97 (0.94-1.06)
log(TNF-αsRII + 1)	1.07 (0.81-1.43)	1.03 (0.84-1.25)	0.92 (0.73-1.16)	1.26 (1.12-1.42)

Estimates also adjusted for study site

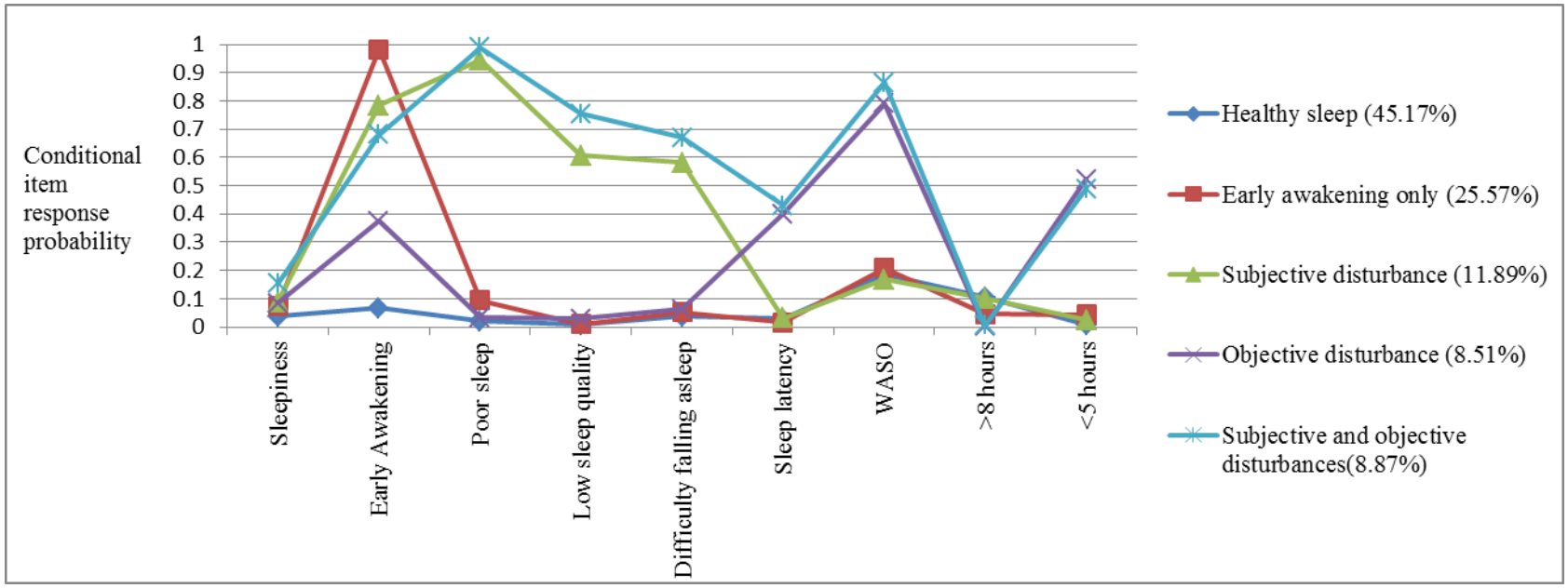

Figure 2. Final LCA model of sleep variables

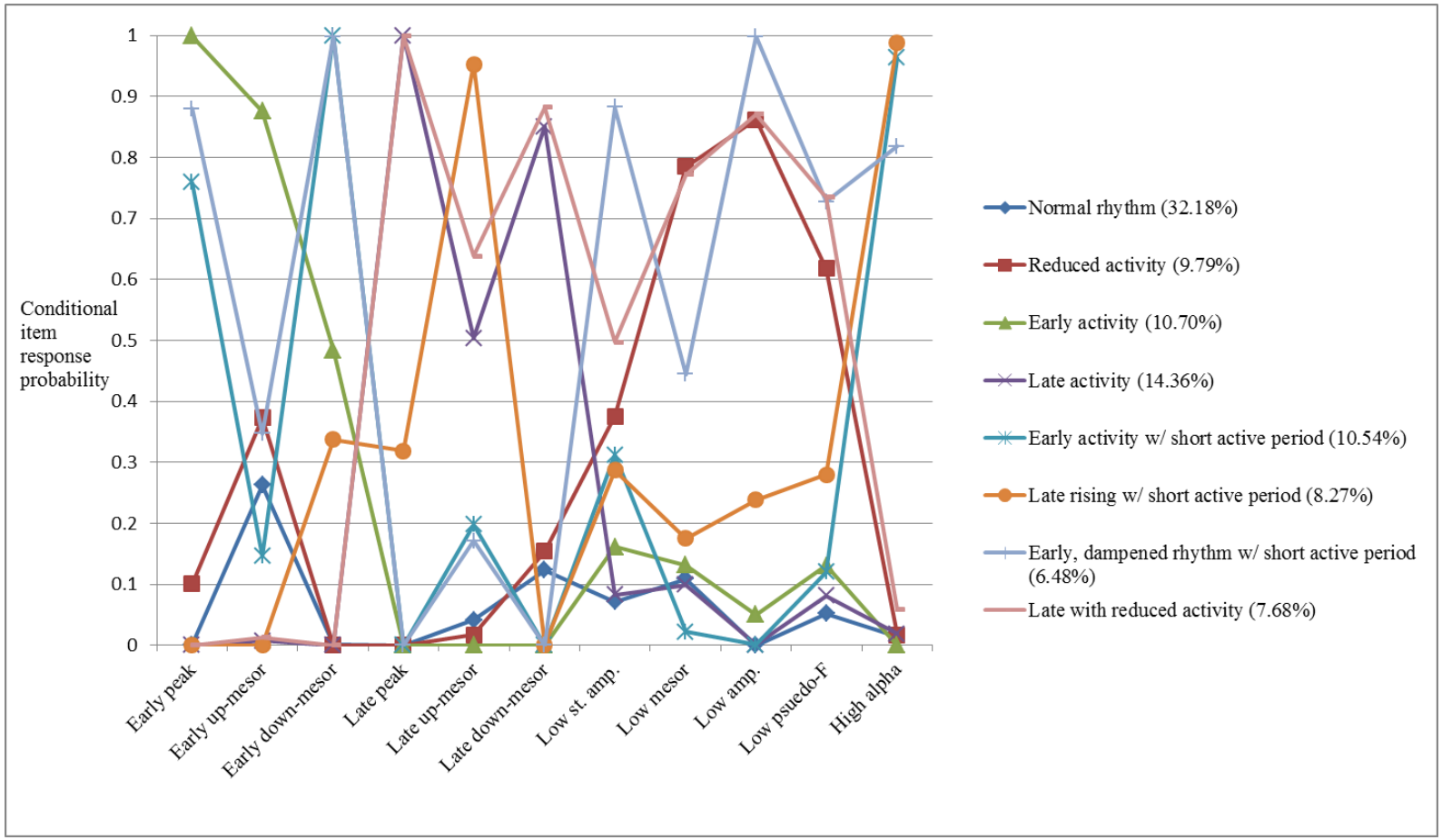

Figure 3. Final LCA model with CAR parameters

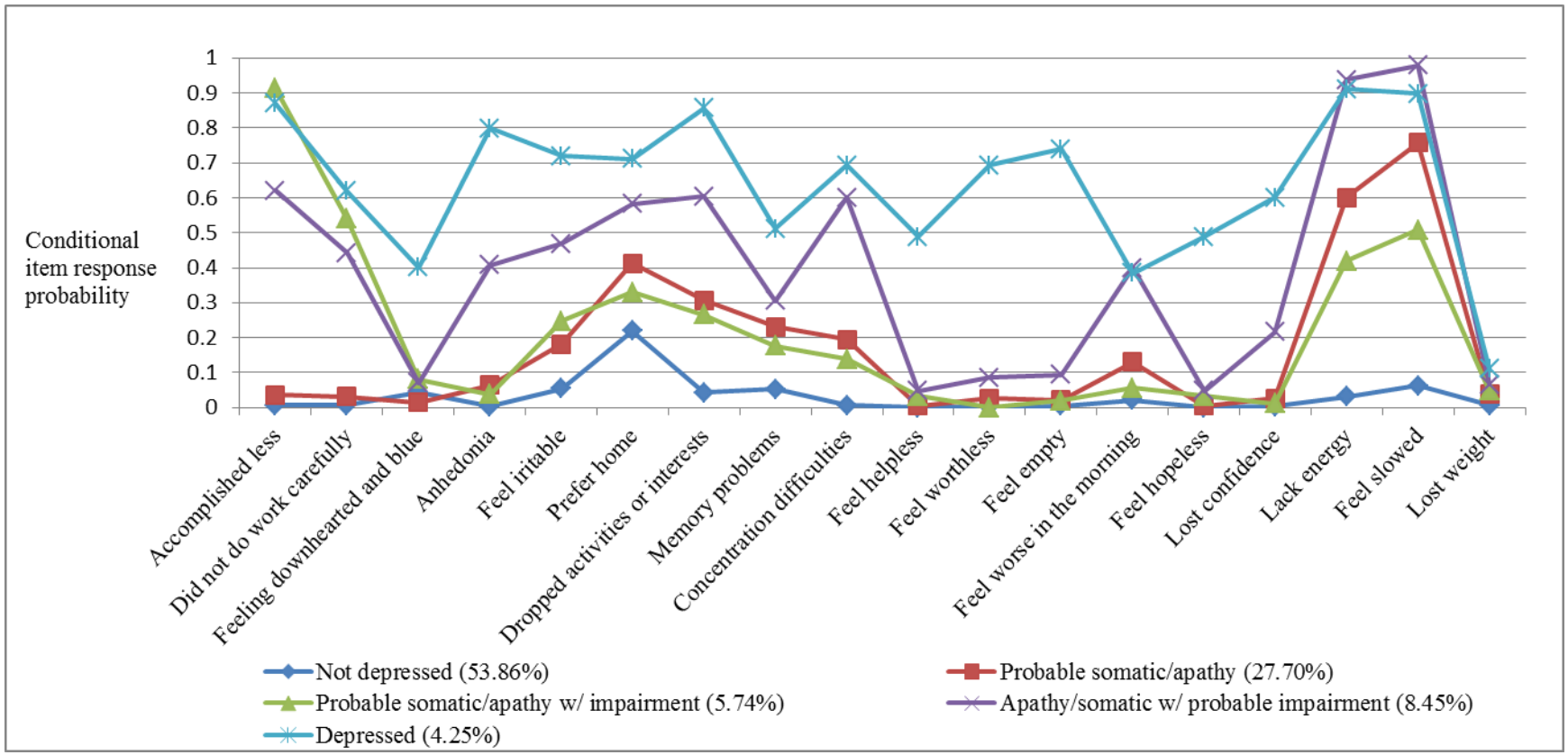

Figure 4. Final LCA model with combined depression items

3.0 LATENT PREDICTORS OF FUTURE CHANGE IN DEPRESSIVE SYMPTOMS AMONG OLDER MEN

In this chapter we examine the relationships between the sleep, CAR, and depressive syndromes (identified in Chapter Two) with future change in overall depression severity. We found that sleep and depressive syndromes were not associated with future levels or change in depressive syndromes. CAR latent classes were independently related to faster rates of change in depressive symptoms overall. Having reduced activity alone was related to faster increases in depressive symptoms, but this relationship was attenuated after covariate adjustment. CAR configurations with later activity, or early activity combined with dampened rhythm and a shortened activity period, were independently related to future increases in depressive symptoms. These associations were independent of, but similar in magnitude to known risk factors, which were also identified in our analysis and included diabetes, a past year fall, and Parkinson's disease. Future research is needed to understand the biological, psychological, and social rhythms and mechanisms related to these novel CAR markers of depression risk.

3.1 INTRODUCTION

Sleep problems have been empirically linked to depression incidence for about 25 years [13]. Arguably one of the most physiologically central of all normal human behaviors, sleep may

be linked to depression development through a wide range of related, multifaceted processes. Problems with sleep are included one of nine symptoms of major depressive disorder (MDD) [15]. Potentially relevant characteristics include the patterning, timing, latency, duration, fragmentation, quality, and electrophysiology of sleep. Because sleep can be a part of and risk factor for depression, understanding the specific aspects involved is both an important scientific and public health priority that can lead to targeted prevention interventions.

These fundamental issues could have the greatest impact among older adults, not only because older adults are a fast growing segment of the population [8], but because they experience sleep problems more often than younger adults [174, 175]. Several studies have demonstrated that among older adults, subjective sleep problems are correlated with incident depressive syndromes ([106, 107, 176-178]). While these studies reliably demonstrate associations between subjectively assessed (self-reported) sleep disturbances and future depression, few reports on the contribution of objectively measured sleep characteristics are available.

In the MrOS Sleep Study, Paudel et al. [107] found that subjective, but not objective, sleep disturbances were associated with future increases in depressive symptoms. In the prior chapter, we determined that subjective and objective disturbances often co-segregate, and we now assess whether these groupings are associated with future changes in depressive symptoms. Based on prior evidence, we hypothesize that subjective, but not objective disturbances will be associated with a faster increases in overall depression severity (reflected as the total scores on the GDS).

We recently found that above and beyond the influence of subjective sleep disturbances, the robustness of daily rest-activity patterns (the CAR) is associated with future increases in

depressive symptoms among MrOS Sleep Study men. This prior analysis, however, was limited by a relatively short (1.2 year) average follow-up period [179]. Furthermore, in our previous work we simply examined the association of individual CAR disturbances with future depression, and we did not assess how specific within-person combinations of CAR characteristics might relate to depression development. We therefore now utilized the CAR groupings from the prior chapter to assess how configurations of CAR disturbances relate to future change in depression severity.

Finally, the question of how pre-existing syndromes or configurations of symptomology relate to depression development spans beyond the sleep health domain. Contemporary MDD criteria reserves diagnoses for severe cases of depression, but does not directly classify clinically meaningful within disorder heterogeneity. The previous chapter demonstrates that, although depressive syndromes clearly vary by symptom burden, individuals with the same symptom count may have different syndromes characterized by distinct symptom patterns (including the presence or absence of psychological symptoms and impairment). Whether these syndromes are linked to future worsening depression severity is unknown. We therefore assess whether commonly occurring depression syndromes are associated with a faster rate of future increases in depression symptoms overall. This may help determine whether mild syndromes characterized by somatic/apathy symptoms are developmental intermediates along the pathway to severe depression.

To assess whether any associations between sleep, CAR, and depression syndromes with future depression are independent of known risk factors, we include a range of covariates previously implicated in the pathogenesis of late-life depression (LLD) spanning from biological

to the social, including chronic diseases, inflammatory markers, disability, stressful life events, and social support.

3.2 METHODS

3.2.1 Participants

The analytic sample is restricted to the MrOS Sleep Study (2003-2005) men described via LCA in Chapter 2 (n=3001). Three follow-up questionnaires were administered in: March 2005-May 2006, March 2007-March 2009, and March 2009-April 2011. Retention was high and complete outcome (GDS) data was available from 99.9%, 97.3%, 88.90%, and 79.37% of baseline participants, respectively. We required participants to have at least complete outcome data at baseline and one other time-point; n=68 failed to meet this criteria and the total unadjusted model therefore included 2933 men. Excluded men tended to be in a latent sleep sub-group characterized by subjective sleep disturbances (Chi-square value = 14.26, df = 4, p=0.007), and they also differed by CAR group (Chi-square value = 17.98, df = 7, p=0.01), and drop-outs appeared to more often have low height or a compressed active period. Men with insufficient longitudinal outcome data did not differ on the basis of their initial LCA depression sub-group (Chi-square value = 5.51 df = 4, p=0.24). Men excluded due to insufficient outcome data also tended to have higher prevalence of certain chronic diseases (i.e. diabetes: Chi-square value=4.81, df=1, p=0.03), past year falls (Chi-square value=8.47, df=1, p=0.004) and were older (mean age 79.54 (6.38 sd) vs. 76.28 (5.48 sd), p<0.0001). No differences in drop-out by race or education were detected.

3.2.2 Measures

3.2.2.1 Primary predictors expressed as individual variables:

When LCA-derived sub-groups were not associated with depression over time, the relevant indicators were modeled as individual variables. Subjective sleep was expressed continuous variable reflecting global sleep quality measured with the Pittsburgh Sleep Quality Index (PSQI) [160] (range 0-21). The self-reported Epworth Sleepiness Scale (ESS) was expressed as a continuous measure of excessive daytime sleepiness ranging from 0 – 24. Objectively assessed variables (including CARs) were expressed exactly as the indicators described in Section 2.2.2.2.

Sleep architecture and sleep disordered breathing (SDB) variables were assessed using polysomnography (PSG) as described in Section 2.2.2.4. Sleep stages (rapid eye movement (REM), stages 1, 2, and slow wave sleep (SWS)) were scored using standard criteria [180] and were expressed as the percentage of sleep time spent in these states. Also included was REM latency, which was defined as the number of minutes from sleep onset to the first REM period. These measures were not included in any LCA and were therefore considered as predictors in all models.

3.2.2.2 Covariates

Age, study site, race, weekly alcohol use, daily caffeine intake, educational attainment, and smoking status were entered as predictors in models of depression levels and change over time. Physical activity, cognitive function, and anxiety symptoms were measured as defined in Section 2.2.2.4.

Psychosocial factors: At MrOS Visit 2, participants were asked whether, over the past 12 months, they had experienced any stressful event included in Table 19. At this time, participants were also administered a questionnaire [181] providing measures of their social networks size and levels of social participation. This including questions regarding if they have living children (yes/no), a special person they feel close to (yes/no), as well as how many relative and friends they have and how many they see at least once per month (response options were 0, 1-2, 3-5, 6-9, or 10+; this variable was entered as a continuous measure reflecting these levels of ranges of increasing social contact). Participants were also asked how many hours per week they participate in groups, and how often they attend religious services (categorical response options were used, see Table 19).

Instrumental Activity of Daily Living (IADL) impairment, chronic diseases, inflammatory markers, and medications were defined as in Section 2.2.2.4.

3.2.3 Statistical methods

The outcome was raw GDS score (including all items) reflecting overall levels of depressive symptoms over time (expressed in years). The GDS is a reliable and valid measure of depression among older adults [155]. Growth curve modeling was implemented using SAS PROC MIXED, an unstructured correlation matrix, and random slopes and intercepts. Separate base models (adjusted for age and study site) assessed crude relationships between latent groups, primary predictors expressed individually, and covariates with the level of depressive symptoms over time; interactions between all predictors/covariates with time (per year) were also included in these base models to assess whether which variables were associated with the rate of change in overall symptomology.

From these separate models, a maximum multivariable was constructed including all associations that achieved at least $p<0.10$ with the level (intercept) or rate of change (slope) in depression symptoms over time. To achieve a parsimonious final model, variables which were not significantly associated with the outcome in the maximum model ($p<0.10$) were removed. Accordingly, only when a latent group predicted change in depression symptoms was it retained in subsequent modeling; otherwise, latent groups were dropped. When a latent group was dropped, the individual measures of the domain were entered if related to depression in crude models.

3.3 RESULTS

The final follow-up assessment was conducted an average of 5.5 years (0.52 SD) after baseline.

Unadjusted associations of covariates with depressive symptoms

Base models indicated that a range of expected factors were significantly associated with the rate of change in depression over follow-up (Table 19). Age was positively associated with both levels and rates of change in depression. Higher educational attainment and levels of self-reported physical activity (PASE) were inversely related to depression levels. Higher BMI, current smoking, and consuming less than one alcoholic beverage per week were all associated with higher levels of depression.

Other mental health factors: Higher levels of cognitive performance (on the 3MS) were related to lower levels of depression and a decreased rate of change over time. Anxiety symptoms were positively associated with levels of depressive symptoms, and were also

associated with a lower rate of change; this finding is likely due to the positive correlation between anxiety and depressive symptoms and a potential ceiling effect on change over time (regression to the mean).

Sleep variables: Higher scores on the PSQI and ESS were related to higher levels of depression. Short sleep duration was associated with higher symptom levels. Long sleep duration and prolong SL were associated with a greater rate of change.

Sleep architecture: Spending a greater percentage of TST in REM sleep was associated with both lower levels of depression and lower rates of change over time. Longer REM latency was associated with higher depression levels. Percentages of time spent in stage 1, stage 2, or SWS were not significantly associated with depression levels of the rate of change.

Stressful events: Separation from someone they depend on, loss of a pet, moved/residence change, serious financial trouble, or any other stressful event were related to higher levels of depression. Spousal/partner serious illness was related to higher rates of change.

Social factors: Having a problem interfere with social activities was related to higher levels but lower rates of change in depressive symptoms. Attending religious meetings and participating in groups more often were both related to lower depression symptom levels; participating in groups ≥16 hours per week was related to lower rates of change. Having living children, a close friend or relatives, and having greater monthly contact with friends/relatives were related to lower levels of depressive symptoms.

Chronic disease: IADL impairment and all chronic diseases (except liver disease), were related to higher levels of depression. The following were additionally related to greater rates of change in depression: falls in the past 12 months, hypertension, diabetes, and Parkinson's disease; severe SDB was associated with higher levels but lower rates of change over time.

Medication use: All medications examined were related to higher levels of depressive symptoms. Antidepressant use was related to higher rates of change in depression, whereas non-benzodiazepine non-barbiturate sedatives/hypnotics were related to lower rates of change in depression.

Inflammatory markers: Except for IFN-γ, all inflammatory markers examined were related to higher levels of depression. In addition, higher levels of TNF-α and TNF-αsRII were associated with higher rates of change in depressive symptoms.

Main analysis: Crude and adjusted associations of latent classes with depression over time

The first unadjusted model (Table 20) included the latent groupings in depression, sleep, and CAR domains (derived in Chapter 2). The depression latent groups were related to levels of symptoms as expected, however there were no meaningful relationships with the rate of change. While the "depressed" group had significantly lower rates of change, this effect reflects a likely ceiling effect or regression towards the mean (patients with depression at baseline had "more room" to improve). The sleep latent sub-groups were also not related to levels or rates of change over time. Therefore these LCA groups were excluded from further analyses.

CAR disturbance sub-groups were all related to faster rates of change in depression over time (compared with the "normal rhythm" group) except for the "early activity" and "early activity with short active period" groups. The "reduced activity" and "early, dampened rhythm with short active period," and "late with reduced activity" groups had higher levels of symptoms over time compared with the "normal rhythm" group.

We assessed whether associations with CAR groups were altered when adjusting for individual sleep and depression variables instead of the representative LCA groups (Table 21);

associations of CAR groups with the rate of change in depression over time were consistent, although associations with the depression intercept were all attenuated to non-significance (this model adjusted for baseline GDS symptoms). Higher levels of baseline depression were related to higher symptom levels and lower rates of change over time. Higher PSQI scores (reflecting worse global sleep quality) were associated with higher symptom levels, and both PSQI scores and long sleep duration were associated with higher rates of change over time.

Further adjustments were added to assess whether the association between depression severity, individual sleep variables, and CAR grouping were independent of covariate associations detected in crude models. The final model (Table 22) included all covariate associations with the level or rate of change that retained significance in the maximum model. Compared with participants included in the final model (n=2700), men excluded appeared to more frequently often to come from CAR groups with delayed or reduced activity, more often had certain chronic diseases (i.e. percentage excluded with Parkinson's = 2.68% compared with included 1.04%, p=0.01), or a past year fall (percentage excluded that fell = 35.43% compared with included 29.58%, p=0.04). Men excluded from the model also tended to be older (age included = 76.99 (6.01 sd) vs. included = 76.28 (5.46 sd), p=0.03) and had higher levels of depressive symptoms at baseline (GDS excluded = 2.07 (2.28 sd) vs. included = 1.74 (2.15 sd), p=0.02).

Covariate adjustment attenuated the association of the "reduced activity" CAR sub-group with higher rates of increase to non-significance. However, the other associations between CAR sub-groups retained significance; specifically, being in any group with late activity ("late activity [only]," "late rising with short active period" and "late with reduced activity") was associated with significantly higher annual increases in depressive symptom load. Being in the "early,

dampened rhythm with short active period" sub-group also remained significantly associated with faster rates of change over time.

Associations between covariates and the levels/rates of change in depressive symptoms over time are shown in Table 22. Note that in the final model, levels of symptoms increased over time and this effect was greater among men who were older. More anxiety symptoms, antidepressant use, having a past year fall, diabetes, and Parkinson's were also associated with faster rates of change. Higher scores on the 3MS (reflecting cognitive function), spending a greater percentage of TST in REM sleep, severe SDB, and benzodiazepine use were related to slower rates of change in depressive symptoms over time.

3.4 DISCUSSION

In our sample, specific configurations of CARs were related to future increases in depressive symptoms independent of physical activity, chronic diseases, and other sleep factors. This finding complements and extends our prior work [179], in part due to the extended follow-up of over 5 years and explicit examination of the overall rate of change symptoms. The primary novel aspect of our analysis is the use of a person-centered, data-driven clustering approach that specified within-person configurations of CAR disturbances related to the development of depressive symptoms.

Although replication in other samples is necessary, we identified CAR configurations which are novel behavioral markers of depression risk. In our study, men with delayed timing or combined early timing with a dampened rhythm and short active period had faster increases in depressive symptoms over time. Having early activity timing alone or in combination with a

compressed active period was not related to future levels of depressive symptoms. Associations between delayed timing and future increases in depressive symptoms were stronger when accompanied by a compressed active period or overall activity reductions. While having reduced activity alone was related to faster increases in depressive symptoms, this association could be explained by covariate adjustments including lifestyle and chronic disease factors.

Although the magnitude of these associations may appear small, comparison with previously established depression risk factors gives context for interpreting the relevance of these novel behavioral markers. The increase in the rate of change associated with CAR sub-groups was equivalent to or greater than the addition risk confirmed by a fall or by diabetes. Therefore, in our study, the depression risk associated with these particular CAR configurations is not only independent of, but it is at least as substantial as known risk factors.

On the other hand, specific sleep or depression syndromes did not predict changes in depression over time. Future research in other samples across different age groups is required to understand whether the impact of sleep factors on depression risk differs across the life course. Our findings also suggest that men with mild depressive syndromes are not at increased risk for faster symptom increases overall. However, these results do not imply that the identified syndromes have wholly similar long term outcomes; we only examined overall changes in depression severity. It is possible that the identified depression syndromes have different outcomes in terms of, for example, risk of physical illness or suicide. Our analysis also did not test whether certain symptoms precede others. Neither did we employ generalized growth mixture modeling which would have enabled us to examine whether LCA group related to distinct patterns of depressive symptom trajectories over time; it is possible that although sleep

and depression symptoms were not related to the overall rate of change, they may relate to specific patterns of change (configurations of symptom intercepts and slopes) over time.

Several limitations should be noted. Although the CAR reflects the activity of the master biological keeper in the suprachiasmic nucleus, it is not a direct indicator of circadian biology. In addition, the CAR is indifferent to psychological and social qualities of rest and activity which may moderate relations to depression over time. The derivation of sub-groups via LCA and subsequent use of these sub-groups to predict change in a longitudinal mixed model introduces measurement error. However, any such bias would potentially reduce the available signal (potency of the true CAR configurations) and bias our results to the null. Our sample consisted of older men who were mostly white and highly educated; therefore these findings cannot necessarily be generalized to other populations.

Other threats to internal and external validity should be considered. The longitudinal analysis method assumes data is missing at random. Our analysis included men who were generally healthier than their counter-parts who did not have complete covariate or adequate outcome data. Participants excluded from the longitudinal models were more likely to be from the CAR groups identified to be at risk; however, if some men who were most at risk for symptom increases were excluded, this could bias/dilute our estimates of the effects of true risk factors towards the null hypothesis. Regarding missing covariate data, we found consistent results in crude (which did not exclude men with missing covariate data) and adjusted models thus suggesting that covariate missing data did not substantively bias or lead to spurious findings. In sum, considering the wide-range of relevant covariate adjustments, our findings appear internally valid. However, these association estimates may not generalize and should be examined in other samples.

In conclusion, specific patterns of CAR disturbance are related to the development of depressive symptoms among older men. Because the CAR is potentially modifiable, future research should test whether interventions targeting the CAR can curtail the burden late-life depression. Future research is required to assess how CAR configurations exert their influence and relate to variability in biological, psychological, and social processes over time. In addition, research investigating the role of circadian rhythms in treatment response is needed to expand our understanding of circadian-depression relations throughout the entire spectrum and course of depressive illness. Finally, given the relevance of CARs to the pathogenesis of depression, future research is needed to understand the developmental history and stability these configurations of CAR disturbances.

3.5 TABLES AND FIGURES

Table 19. Crude associations of covariates with the intercept and slope of depressive symptoms over time

				Predictor * Time		
	β	SE	p	β	SE	p
Age (per SD)	**0.33**	**0.04**	**<0.0001**	**0.06**	**0.01**	**<0.0001**
Study Site:						
BI	**0.42**	**0.13**	**0.0012**	**0.02**	**0.03**	**0.54**
MN	**-0.11**	**0.13**	**0.37**	**0.04**	**0.03**	**0.16**
PA	**-0.32**	**0.13**	**0.01**	**0.06**	**0.03**	**0.04**
PI	**0.28**	**0.13**	**0.03**	**0.07**	**0.03**	**0.01**
PO	**0.03**	**0.13**	**0.80**	**0.02**	**0.03**	**0.58**
SD		Reference				
Race:						
White	-0.27	0.16	0.10	0.01	0.03	0.83
Black	0.23	0.25	0.36	-0.07	0.05	0.19
Other		Reference			Reference	
Alcohol use per week:						
<1 drink	**0.35**	**0.17**	**0.04**	-0.04	0.03	0.20
1-13 drinks	0.08	0.17	0.65	-0.04	0.03	0.21
14+ drinks		Reference			Reference	
Daily caffeine intake (per SD)	-0.03	0.04	0.47	-0.005	0.01	0.53
Education:						
Less than high school	**0.64**	**0.17**	**0.0003**	**0.03**	**0.04**	**0.34**
High school diploma	**0.19**	**0.11**	**0.09**	**0.05**	**0.02**	**0.02**
College/Graduate school		**Reference**			**Reference**	
Smoking Status:						
None	**-1.15**	**0.28**	**<0.0001**	-0.05	0.06	0.34
Former	**-0.97**	**0.28**	**0.001**	-0.02	0.06	0.67
Current		Reference			Reference	
BMI (per SD)	**0.15**	**0.04**	**0.0001**	-0.003	0.01	0.72
Physical Activity (per SD)	**-0.40**	**0.04**	**<0.0001**	0.004	0.01	0.58
Cognitive function (per SD)	**-0.24**	**0.04**	**<0.0001**	**-0.04**	**0.01**	**<0.0001**

Table 19 continued

Anxiety symptoms	**0.52**	**0.02**	**<0.0001**	**-0.02**	**0.004**	**0.0002**
PSQI (continuous)	**0.22**	**0.01**	**<0.0001**	**-0.004**	**0.002**	**0.07**
Epworth (continuous)	**0.10**	**0.01**	**<0.0001**	-0.001	0.002	0.69
WASO	**0.33**	**0.08**	**<0.0001**	0.01	0.02	0.55
SL	-0.01	0.03	0.58	**0.64**	**0.13**	**<0.0001**
Sleep duration						
<5	**0.31**	**0.12**	**0.008**	0.03	0.02	0.26
5-8			Reference			Reference
>8	0.06	0.15	0.68	**0.07**	**0.03**	**0.03**
Sleep architecture						
% TST in Stage 1	0.007	0.01	0.477	0.003	0.002	0.153
% TST in Stage 2	0.007	0.004	0.094	0.00001	0.001	0.99
% TST in Stage 3/4	0.002	0.004	0.623	0.001	0.001	0.31
% TST in REM	**-0.02**	**0.01**	**0.0003**	**-0.003**	**0.001**	**0.03**
REM Latency (minutes)	**0.003**	**0.001**	**<.0001**	0.00004	0.00011	0.68
Recent Stressful events						
Serious illness or accident of wife or partner	0.18	0.10	0.07	**0.04**	**0.02**	**0.05**
Death of other close relative or close friend	0.08	0.08	0.29	0.01	0.02	0.38
Separation from child, close friend, or other relative who participant depends on	**1.09**	**0.24**	**<0.0001**	0.03	0.05	0.60
Loss of a pet	**0.45**	**0.16**	**0.01**	-0.05	0.03	0.13
Moved or changed in residence	**0.83**	**0.17**	**<0.0001**	**-0.06**	**0.04**	**0.09**
Serious financial trouble	**1.61**	**0.22**	**<0.0001**	-0.07	0.05	0.13
Anything else important happen	**0.47**	**0.08**	**<0.0001**	0.01	0.02	0.50
Social Factors						
Physical or emotional problem interfered more with social activities	**1.36**	**0.05**	**<0.0001**	**-0.03**	**0.11**	**0.003**
How often go to religious meetings?						
More than once per week	**-0.66**	**0.11**	**<0.0001**	-0.02	0.02	0.27
Once per week	**-0.47**	**0.10**	**<0.0001**	0.01	0.02	0.56
1-3 times per month	**-0.30**	**0.14**	**0.04**	0.04	0.03	0.21
Less than once per month	**-0.11**	**0.15**	**0.48**	-0.04	0.03	0.16
Never or almost never		Reference			Reference	
How many hrs/wk participate groups?						
16 or more	**-0.98**	**0.19**	**<0.0001**	**-0.08**	**0.04**	**0.04**
11-15	**-0.90**	**0.21**	**<0.0001**	-0.004	0.04	0.93

Table 19 continued

6-10	**-0.85**	**0.12**	**<0.0001**	-0.02	0.03	0.46
3-5	**-0.61**	**0.11**	**<0.0001**	-0.02	0.02	0.26
1-2	**-0.39**	**0.10**	**0.0001**	-0.001	0.02	0.97
None		Reference			Reference	
Has living children	**-0.41**	**0.15**	**0.01**	0.01	0.03	0.87
Has special person feels close to	**-0.81**	**0.12**	**<0.0001**	-0.01	0.02	0.62
Number of close relatives	**-0.18**	**0.03**	**<0.0001**	-0.01	0.01	0.28
How many relatives participants sees once per month	**-0.12**	**0.04**	**0.002**	0.001	0.01	0.81
Number of close friends	**-0.35**	**0.03**	**<0.0001**	**0.01**	**0.01**	**0.07**
How many close friends participant sees once per month	**-0.33**	**0.03**	**<.0001**	0.003	0.01	0.61
<u>Chronic Disease History</u>						
IADL Impairment (per additional impairment)	**0.81**	**0.04**	**<0.0001**	0.01	0.01	0.21
Fall in past 12 months	**0.68**	**0.08**	**<0.0001**	**0.03**	**0.02**	**0.07**
Peripheral vascular disease	**0.77**	**0.13**	**<0.0001**	-0.01	0.03	0.70
Osteoarthritis	**0.68**	**0.09**	**<0.0001**	-0.01	0.02	0.59
Rheumatoid Arthritis	**0.91**	**0.14**	**<0.0001**	0.04	0.03	0.17
Hypertension	**0.29**	**0.76**	**0.0001**	**0.03**	**0.02**	**0.08**
Stroke	**1.02**	**0.20**	**<0.0001**	0.05	0.04	0.27
Angina	**0.61**	**0.11**	**<0.0001**	0.01	0.02	0.67
Congestive Heart Failure	**0.58**	**0.16**	**0.0004**	0.03	0.04	0.42
Myocardial Infarction	**0.41**	**0.10**	**<0.0001**	0.03	0.02	0.15
Diabetes	**0.29**	**0.11**	**0.01**	**0.06**	**0.02**	**0.01**
COPD	**1.01**	**0.17**	**<0.0001**	0.02	0.04	0.57
Parkinson's	**1.91**	**0.34**	**<0.0001**	**0.25**	**0.07**	**0.0006**
Renal disease	**0.86**	**0.39**	**0.03**	0.04	0.09	0.64
Cataracts	**0.22**	**0.08**	**0.005**	0.01	0.02	0.48
Liver disease	0.20	0.27	0.46	-0.06	0.05	0.26
Severe sleep disordered breathing (AHI ≥ 30)	**0.28**	**0.10**	**0.01**	**-0.04**	**0.02**	**0.05**
<u>Medication Use</u>						
Antidepressant use	**1.69**	**0.14**	**<0.0001**	**0.05**	**0.03**	**0.10**
Non-benzodiazepine non-barbiturate sedatives /hypnotics	**0.89**	**0.27**	**0.001**	**-0.15**	**0.05**	**0.01**
Benzodiazepines use	**1.22**	**0.18**	**<0.0001**	0.01	0.04	0.73
Current NSAID use	**0.34**	**0.95**	**0.0003**	-0.001	0.02	0.69

Table 19 continued

corticosteroid use (oral/nasal/inhaled)	Current	**0.34**	**0.13**	**0.01**	0.04	0.03	0.15
Inflammatory Markers							
log(IL-6 + 1)		**0.26**	**0.09**	**0.0033**	0.03	0.02	0.18
log(CRP + 1)		**0.22**	**0.06**	**0.0004**	-0.01	0.01	0.45
log(TNF-α + 1)		**0.40**	**0.15**	**0.01**	**0.06**	**0.03**	**0.06**
log(TNF-αsRII + 1)		**0.54**	**0.12**	**<0.0001**	**0.08**	**0.02**	**0.0006**
log(IFN-γ + 1)		-0.04	0.07	0.58	0.02	0.01	0.24

*Base model includes age and study site

Table 20. Crude associations of combined sleep/depression and CAR latent class membership with the intercept and slope of change in depressive symptoms (n=2933)

				Predictor * Time		
	β	SE	p	β	SE	p
Depression Latent Class						
Depressed	**6.96**	**0.12**	**<0.0001**	**-0.45**	**0.04**	**<0.0001**
Apathy/somatic with probable impairment	**3.23**	**0.10**	**<0.0001**	-0.02	0.03	0.52
Probable somatic/apathy with impairment	**1.48**	**0.10**	**<0.0001**	-0.004	0.03	0.90
Probable apathy/somatic	**1.41**	**0.06**	**<0.0001**	0.01	0.02	0.45
Not depressed	Reference			Reference		
Sleep Latent Class						
Subjective and objective disturbances	0.17	0.11	0.13	-0.02	0.04	0.55
Objective disturbances	0.005	0.09	0.96	0.03	0.03	0.37
Subjective disturbances	0.08	0.08	0.33	0.01	0.02	0.76
Early awakening	-0.06	0.06	0.34	0.02	0.02	0.29
Healthy sleep	Reference			Reference		
Circadian Activity Rhythm Latent Class						
Normal rhythm	Reference			Reference		
Reduced activity	**0.28**	**0.09**	**0.001**	**0.06**	**0.03**	**0.03**
Early activity	0.13	0.08	0.11	-0.02	0.03	0.47
Late activity	-0.04	0.08	0.63	**0.05**	**0.02**	**0.04**
Early activity with short active period	0.16	0.09	0.06	0.02	0.03	0.47
Late rising with short active period	0.07	0.09	0.42	**0.10**	**0.03**	**0.001**
Early, dampened rhythm with short active period	**0.26**	**0.10**	**0.01**	**0.11**	**0.03**	**0.002**
Late with reduced activity	**0.23**	**0.10**	**0.02**	**0.10**	**0.03**	**0.002**

*Crude model includes age and site

Table 21. Crude associations of CAR latent class membership plus individual parameters with the intercept and slope of change in depressive symptoms (n=2929)

				Predictor * Time		
	β	SE	p	β	SE	p
Baseline symptom level	0.89	0.01	**<0.0001**	**-0.06**	**0.004**	**<0.0001**
PSQI (continuous)	**0.01**	**0.01**	**0.01**	**0.01**	**0.003**	**0.01**
WASO≥90	0.05	0.04	0.23	0.02	0.02	0.38
SL≥60	-0.001	0.06	0.93	-0.02	0.03	0.55
Sleep duration (hours)						
<5	-0.02	0.06	0.71	0.02	0.03	0.47
5-8	Reference			Reference		
>8	-0.02	0.06	0.77	**0.06**	**0.03**	**0.05**
Circadian Activity Rhythm Latent Class						
Normal rhythm	Reference			Reference		
Reduced activity	0.01	0.06	0.85	**0.10**	**0.03**	**0.0008**
Early activity	0.01	0.06	0.81	-0.02	0.03	0.52
Late activity	-0.01	0.05	0.86	**0.05**	**0.02**	**0.04**
Early activity with short active period	0.06	0.06	0.29	0.02	0.03	0.51
Late rising with short active period	0.04	0.06	0.51	**0.10**	**0.03**	**0.0016**
Early, dampened rhythm with short active period	0.05	0.07	0.48	**0.13**	**0.03**	**0.0002**
Late with reduced activity	0.02	0.07	0.79	**0.13**	**0.03**	**<0.0001**

*Crude model includes age and site

Table 22. Adjusted associations of individual predictors with the intercept and slope of change in depressive symptoms from the final model (n=2700)

				Predictor * Time		
	β	SE	p	β	SE	p
Intercept	**1.06**	**0.20**	**<0.0001**			
Time (per year)	**0.50**	**0.10**	**<0.0001**			
Baseline symptom level	**0.87**	**0.01**	**<0.0001**	**-0.07**	**0.004**	**<0.0001**
Circadian Activity Rhythm Latent Class						
Normal rhythm					Reference	
Reduced activity				0.04	0.03	0.21
Early activity				-0.02	0.03	0.47
Late activity				**0.05**	**0.02**	**0.03**
Early activity with short active period				0.01	0.03	0.65
Late rising with short active period				**0.06**	**0.03**	**0.03**
Early, dampened rhythm with short active period				**0.09**	**0.03**	**0.01**
Late with reduced activity				**0.07**	**0.03**	**0.02**
Demographic and Lifestyle						
Age (per SD)	0.04	0.02	0.05	**0.06**	**0.01**	**<0.0001**
BMI (per SD)	0.03	0.02	0.06			
Physical activity (per SD)	0.03	0.02	0.07			
Other mental health						
Cognitive function (per SD in 3MS score)				**-0.04**	**0.008**	**<0.0001**
Anxiety symptoms				**0.02**	**0.005**	**0.0006**
PSQI (continuous)	**0.01**	**0.01**	**0.03**			
% time REM				**-0.003**	**0.002**	**0.02**
Stressful events						
Loss of a pet	**-0.15**	**0.07**	**0.03**			
Separated from child who is depended on	0.19	0.10	0.06			
Serious financial trouble	**0.21**	**0.10**	**0.03**			
Anything else important happen	**0.16**	**0.03**	**<0.0001**			
Social Factors						
How many hrs/wk participate groups?						
16 or more	**-0.24**	**0.09**	**0.01**	**-0.10**	**0.04**	**0.01**
11-15	**-0.26**	**0.09**	**0.01**	-0.05	0.04	0.21
6-10	**-0.19**	**0.05**	**0.0005**	-0.04	0.03	0.14
3-5	**-0.16**	**0.05**	**0.0008**	**-0.04**	**0.02**	**0.04**
1-2	**-0.08**	**0.04**	**0.08**	-0.01	0.02	0.49
0		Reference			Reference	
Number of relatives	**-0.05**	**0.01**	**0.0012**			
Chronic Disease						
IADL Impairment (per additional impairment)	**0.08**	**0.02**	**0.0009**			
COPD	0.11	0.07	0.15			
Fall in past 12 months				**0.05**	**0.02**	**0.003**
Diabetes				**0.07**	**0.02**	**0.004**
Parkinson's				**0.26**	**0.08**	**0.0008**

Table 22 continued

Severe SDB				**-0.06**	**0.02**	**0.01**
Medication Use						
Antidepressant use	**0.17**	**0.07**	**0.01**	**0.10**	**0.03**	**0.0011**
Benzodiazepine use				**-0.13**	**0.05**	**0.01**
Non-benzodiazepine non-barbiturate sedatives/hypnotics	0.16	0.08	0.06			

4.0 PHARMACOLOGICAL RESPONSE IN LATE-LIFE MAJOR DEPRESSIVE DISORDER AND ASSOCIATED PROGNOSTIC FACTORS

Depression severity may be causally related to treatment resistance among the over 50% of older adults who fail to recover after an antidepressant trial. However, no current evidence demonstrates whether high levels of baseline symptoms are a necessary component of poor treatment response. In addition, limited prior research examines whether differential symptom expression or specific aspects of cognitive function are related to treatment outcomes. We examined these prognostic factors in an open-label pharmacological (venlafaxine XR) treatment study conducted among adults aged ≥60 years who had major depressive disorder (n=453). Group-based trajectory analysis was used to derive sub-groups exhibiting similar patterns of symptom change over 12 weeks. Distinctly remitting groups were detected across lower (15.23%), moderate (23.84%), and higher (5.52%) baseline symptom levels. Persistent trajectories were most common among patients with higher baseline symptom levels (totaling 35.98%), however, a group with relatively moderate symptoms at baseline also followed mixed/non-responsive trajectory (19.43%). The prognostic factors significantly associated with less favorable trajectories included greater overall symptom burden, longer episode duration, past adequate antidepressant treatment, less reduced sleep, more guilt and work/activity impairment. Higher scores on a list-recognition test were associated with a more rapid response. Although not necessarily generalizable to younger adults or other treatments/settings, these

findings show that treatment response is heterogeneous across a range of baseline symptoms levels. Future research is needed to understand the biological basis of the identified prognostic factors and to develop predictive algorithms for early detection of treatment resistance in clinical settings.

4.1 INTRODUCTION

The epidemiologic study of prognostic factors in geriatric mental health is important, not only to improve detection and targeted prevention approaches, but also to support clinical treatment allocation strategies for late-life major depressive disorder (LLD). Depression is most often treated in primary care [49, 182], however over 50% of older adults fail to respond to first-line antidepressant treatment [183, 184]. In part due to substantial pre-treatment co-morbidity [185] and polypharmacy [186], pharmacological treatment can be particularly complex and time consuming among older adults [187-189]. Initial antidepressant treatment success rates (i.e. 28% in the STAR*D trial) may improve to up to 70% after multiple drug trials by one year, but as described by National Institute of Mental Health director Thomas Insel, M.D., current expectations for antidepressant success may have been set “far too low” [190]. Improving our understanding of the patterns of pharmacological treatment response and associated prognostic factors can guide clinical approaches to accurately anticipate treatment response variability and decrease the time before recovery.

Early detection of treatment resistant LLD can save time, money, and suffering by informing when clinicians should “stay the course” and when first-line treatment will inevitably fail (and a new treatment strategy will need to be employed) [189, 191]. Treatment failure

mechanisms are not understood although a range of clinical and neurobiological factors have been linked to treatment failure. Research has not yet arrived upon a clinically actionable description of the measureable aspects of resistance as it appears at treatment intake. Such description would give hints towards the determinants of treatment response variability and could lead to early detection strategies.

Prior research demonstrates that certain clinical characteristics and early change in certain factors predict overall treatment response and stability [189, 192]. In recent evidence from a prospective evaluation of treatment resistance in the Incomplete Response in Late-Life Depression (IRLGREY) Study, several prognostic factors were identified, including: total symptom burden and its early change, episode duration, and prior history of adequate antidepressant treatment [183]. In this analysis of IRLGREY, the most powerful prognostic predictors were overall baseline and early changes to overall symptom severity.

These findings suggest a role of baseline symptom load in the etiology of treatment resistance, however this may be an artifact of outcome definition. Often studies define remission as achievement of a pre-specified total symptom level after a certain time period (i.e. a Montgomery Asberg Depression Rating Scale [28] (MADRS) score of $\leq$10 after 12 weeks of treatment). The etiological interpretation afforded by this outcome definition is limited, because, depending on initial symptom level, two patients recovering at the exact same rate may or may not reach the remission threshold within a timeframe. Therefore, while pre-specified remission criteria are essential to secure a clinically valid response definition, they alone may obscure the causal picture regarding whether a high symptom burden is a component or a *necessary* component of treatment non-response.

An alternative technique to study treatment response is to identify distinct sub-groups of individuals based on their pattern of change in symptom level over time. Despite widespread use including investigations of late-life depression's course among community-dwelling older adults [193-197], less research has applied group-based clustering techniques to understand patterns of change in pharmacological treatment for LLD. Longitudinal clustering techniques have been applied to examine patient trajectories in primary care [198], in heart failure patients [199], after combined psychotherapy and pharmacotherapy [200-202], and in relation to pharmacogenomics markers of response to either nortriptyline or escitalopram [203]. Other studies have utilized longitudinal clustering techniques to examine heterogeneity in response to solo pharmacological treatment [203-205]. These studies often conclude that such methods capture heterogeneity across the course of treatment that could be neglected using pre-specified response thresholds or other methods which assume the patient population follows a single response trajectory.

To my knowledge, this is the first application of group-based trajectory modeling to a large (several hundred) sample of older adults undergoing solo pharmacological treatment. We aim to add detail to descriptions of expected [183, 184] heterogeneity in treatment response patterns. Depending on whether heterogeneity in response is detected across a range of baseline symptom levels, this may suggest if a high burden of baseline symptoms is a necessary or sufficient condition for treatment resistance.

We also aim to provide a comprehensive description of the prognostic factors associated with treatment response trajectories. Specific domains of cognition have been implicated in the etiology of treatment resistance. Some have suggested that executive function in particular predicts treatment response [206-208]; and a recent study reported that even complaints of executive function were predictive [209]. Information processing speed, which may be the core

cognitive process on which other cognitive domains (including executive function) depend [210], has also been associated with treatment response [211, 212].

In addition to overall severity and cognitive performance, disproportionate expression of depression symptoms may have a role determining treatment resistance. Early change in core symptoms have recently been associated with treatment response [213]. Sparse evidence demonstrates that sleep symptoms may be an important determinant/proxy measure of response [202].

In current analysis we examine the patterns of treatment response observed among a large sample of older adults undergoing open label Venlafaxine XR (Effexor) treatment for LLD. We estimate the prevalence of distinct patterns of longitudinal change, and also extend prior work [183] by examining whether specific depressive symptoms, domains of cognitive functioning, and other clinical variables are associated with treatment response variability.

4.2 METHODS

4.2.1 Participants

Details of recruitment have been described previously [183]. Recruitment sources included primary and specialty care referrals, advertisement responses, research registry based solicitation. Participants were aged ≥60 (n=466) and had current nonpsychotic major depressive disorder as diagnosed by the Structured Clinical Interview for DSM-IV [23] plus a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥15. Exclusions were: lifetime diagnosis of bipolar disorder, schizophrenia, schizoaffective, other psychotic disorders or current psychotic

symptoms; clinical history of dementia or cognitive impairment as indicated by a score of <20 on the Mini Mental Status Exam [214]; alcohol or substance abuse in the past 3 months; high suicide risk; unstable medical illness; or contraindication to venlafaxine XR or aripiprazole. For this analysis, participants were included if they had complete outcome data from baseline and at least one follow-up visit (n=453). All participants provided informed consent and ethical approval was obtained from institutional review boards across participating sites.

4.2.2 Intervention

The open-label trial being examined was conducted to prospectively establish treatment resistance for a subsequent randomized trial of an adjunctive therapy for treatment resistant LLD. Participants in the open-label trial were treated with Venlafaxine XR for 12 weeks, stating at 37.5 mg/day and titrated in increments (of 37.5 mg) at least every 3 days. By the end of week 6, patients with MADRS scores >10 had their dose increased further in 37.5-75 mg increments every 3 days to a target of 300 mg/day dose. Further details regarding use of other medications has been published previously [183]. Pharmacological treatment was delivered within a model of depression management including supportive clinical care focused on psychoeducation about depression, its symptoms and treatment, suicidal ideation, countermeasures for adverse medication effects, and treatment adherence. Depression-specific psychotherapy was not provided.

4.2.3 Outcome measures

Depression symptom burden was measured over time as the total MADRS score assessed at study baseline, week 1, week 2, and every two weeks thereafter until the completion of the open-label study at 12 weeks.

4.2.4 Potential prognostic factors

Baseline assessments also included the 17 item Hamilton Rating Scale for Depression (HRSD-17) [215]. Both the MADRS and HRSD-17 were examined as scored totals as well as individual items in order to assess potential prognostic roles of both overall symptom burden and individual symptoms.

Adequacy of prior antidepressant treatment was measured with the Anti-depressant Treatment History Form (ATHF) [216] where scores ≥3 indicate a prior adequate trial. Age at onset of first depressive episode, duration of current episode (natural-log transformed), single vs. recurrent episodes, and any outside psychotherapy during participation were also considered. The Scale for Suicidal Ideation (SSI) [217] was used to measure suicidal ideation. The Brief Symptom Inventory (BSI) [218] were used to assess general anxiety symptoms. Medical comorbidity was assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [219] examined as a total score, count, and individual items (coded as ≥2 to reflect the presence of organ system dysfunction). The physical function sub-section of the 36-item Medical Outcomes Study Short-From Health Survey (SF-36 Physical) was expressed as a total score [220]. Alcohol use was assessed as the self-reported number of drinks per week.

Neuropsychological measures administered at baseline included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [221]. We initially examined RBANS Index Scores; when potential prognostic differences were detected, we investigated the component subtests to assess associations of domain-specific neuropsychological performance with response. Analyses of RBANS subtest scores were conducted after computing age normed Z-scores. Two tasks from the Delis-Kaplan Executive Function System (D-KEFS) [222] were examined in a similar manner.

4.2.5 Statistical methods

A semiparametric, group-based modeling strategy was used to classify the cohort into sub-cohorts based on identifying heterogeneous longitudinal polynomial trajectories [223, 224]. The sub-groups are sometimes referred to as latent classes or trajectories. We implemented this technique using PROC TRAJ [224] in SAS version 9.3 (SAS Institute Inc., Cary, NC). Our implementation employed a censored normal distribution and the number and degree of trajectory groups was determined using the Bayesian information criterion (BIC).

The BIC measures improvement in model fit gained by adding additional groups or shape parameters incorporating a penalty for added complexity. BIC log Bayes factor approximation, defined as 2 times ΔBIC (subtracting a less complex from a more complex model), was used to base selection of the number of trajectory groups which fit the data; BIC log Bayes factor approximation of >10 is considered strong evidence in favor of the more complex model [224]. Solutions that identified small (<5% of the sample) trajectory groups were rejected. When initially assigning all groups linear, quadratic, and cubic trajectories, BIC consistently indicated the same optimal number of groups. The degree of the fitted polynomials was determined by

examining BIC for all possible permutations of group exponents. We also used a step-down model fitting strategy, that is, we started with all trajectories being cubic polynomials and sequentially decreased the polynomial degree until all parameters associated with the highest degree of polynomial were statistically significant. The two strategies yield the same solution for the curve fits. We then examined the average posterior probability (>70% recommended) and odds of correct classification (OCC; >5 considered adequate) as model fit heuristics.

Trajectory groups were compared outside of the PROC TRAJ framework to select predictors using weighted multi-nominal logistic regression; these regressions were down-weighted by the probability of group membership to account for measurement error introduced by the probabilistic nature of group assignment. To determine whether trajectory group membership was associated with the severity of individual depression symptoms independent of overall symptom severity (which was investigated in its own right) we examined associations of individual symptoms with trajectory group after adjusting for total baseline depression severity as measured using the item's scale's total score (MADRS or HRSD-17). Associations of group membership with prognostic factors that achieved statistical significance (defined as $p<0.05$) were selected as predictors in a maximum model. We applied automated backwards elimination (elimination threshold $p>.20$) to select uniquely predictive prognostic factors which were then entered as baseline risk factors within the PROC TRAJ framework. The reference group was chosen to represent the largest group with a distinct response.

4.3 RESULTS

4.3.1 Model selection and trajectory groups

Model fit indicated with BIC continuously improved with additional trajectory groups (Table 23), however a seven-group solution included a small (<5%) group. BIC log Bayes factor approximation indicated strong evidence that a six-group solution fit the data better than a five-group solution. The data was best fit by a combination of linear and quadratic trajectory groups (see below).

This model detected heterogeneity in response trajectories *across all levels of baseline depressive symptoms* (Figure 5). Average posterior probabilities were high for all six groups (range: 0.84-0.90; Table 24), and the OCC were all well above 5 (minimum OCC=20.18). Spaghetti plots by trajectory group are shown in Figure 6. Groups were labeled according to their relative starting position and trajectory over time. Two groups with quadratic trajectories of change started at relatively lower and moderate levels before remitting (15.23% (n=68) “rapid response”; 23.84% (n=108) “moderate, response”); an additional group with a higher level of symptoms followed a linear trajectory of change and remitted (5.52% (n=25) “high, response”). A second group starting with moderate symptom levels followed a linear trajectory, but maintained the majority of their symptoms (19.43% (n=88) “moderate, mixed/non-response”). One group started high and followed a linear trajectory of change which ended with still high depression severity (24.28% (n=110) “high, non-response 1”), whereas the last group started high and followed a persistent pattern with a linear slope (11.7% (n=53) “high, non-response 2”).

4.3.2 Predictor selection

Age was related to trajectory group membership ($p<0.0001$), and it appeared that generally groups with higher baseline symptom levels were younger (Table 25). The following were also related to trajectory group membership: age at first episode, episode duration, prior adequate antidepressant trial, SF-36 physical health, and BSI anxiety scores. No significant relations were detected between count, total, or individual CIRS-G items with trajectory group.

All individual depression symptoms were significantly related to trajectory group before adjusting for total symptom level (all $p<0.05$). These differences individual symptom severity levels appeared to be a function of overall symptom load and did not clearly differ by whether the trajectory group remitted. We therefore examined associations adjusted for total baseline symptom severity. After this adjustment, the only MARDS item significantly associated with trajectory group was the baseline symptom "reduced sleep" ($p=0.0085$). From the HDRS-17 items, trajectory group membership was significantly associated with two items: "depressed mood" ($p=0.0059$), "feelings of guilt" ($p=0.0077$), "work and activities" ($p=0.0096$), and "agitation" ($p=0.0026$).

Neuropsychological characteristics were not associated with group membership except for performance in the delayed memory and language domains of the RBANS (Table 26). Higher performance in the language domain was related to lower odds of membership in all three of the less favorable trajectories; higher performance in the delayed memory domain was related to higher odds of being in the "rapid response" group.

4.3.3 Adjusted associations of prognostic factors with group membership

The above mentioned factors were entered into a maximum, weighted multinomial logistic regression model. Associations that retained significance were entered into the PROC TRAJ framework as baseline risk factors. In the final model (Table 27), higher baseline depression severity was related to 44% lower the odds of being in the “rapid response” compared with the “moderate, response” group. Each standard deviation higher in list recognition performance (a sub-test from the delayed memory domain of the RBANS) was associated with 2.22 times the odds of being a “rapid responder” (all comparisons are with the “moderate, response” group). Baseline MADRS were positively associated with being in the “high, response” group, but no other prognostic factors correlated with membership in this group.

Higher depression severity overall (total MADRS) and for the MADRS “reduced sleep” item were associated with lower odds of being in the “moderate, mixed/non-response” group. Baseline MADRS scores were positively associated with the odds of membership in both “high, non-response” groups; however, baseline levels of “reduced sleep” were negatively associated with being in these non-responsive groups.

Longer episode duration was related to 54% higher odds of being in the “high, non-response 1” group, while greater education was related to 17% decreased odds of being in this group; greater levels of guilt were marginally ($p=0.0554$) associated with higher odds of membership in this treatment resistant group. Higher levels of work/activity impairment and guilt were both associated with substantially greater odds of being in the other treatment resistant group (“high, non-response 2” group). Each standard deviation higher list-recognition performance was also associated with 33% lower odds of being in the second non-responding group (although this association failed to achieve statistical significance; $p=0.0795$).

4.4 DISCUSSION

Using group-based trajectory modeling, our analysis illustrates the specific treatment response patterns found across the entire range of baseline symptom severity. We detected a group of patients who clearly remitted following Venlafaxine XR treatment. These responders (44.59% across the range of baseline symptom load) were in similar proportion to prior research [183], and this convergence adds validity to our data-driven endeavor.

Patients with higher baseline depression severity generally experienced a lack of symptom relief, and this finding suggests that high symptom severity is associated with treatment resistance. However, we also noted a group ("high, response") with severe baseline symptoms that appeared to remit, thus, severity alone may be an insufficient cause of treatment resistance. Additionally, we found symptom persistence among the "mixed, non-response" group, suggesting that beginning treatment in the upper symptom range is not a necessary (though perhaps a common) causal component of treatment resistance.

In the final multivariable model, self-report of more severely reduced sleep was associated with favorable response patterns. We also found that higher levels of guilt were associated with increased odds of having persisting symptoms, as were greater levels of work/activity impairment (for the second treatment resistant group). Venlafaxine XR may be particularly efficacious for patients with relatively high levels of subjective sleep deficits and low levels of guilt and work/activity impairment. It is important to also note that the three sleep items on the HRDS-17 indicating early, middle, and late insomnias were not associated with trajectory group (other than as a function of overall symptom severity). To clarify the meaning of these results, future examinations should include comprehensive/objective sleep assessments.

Prolonged episode duration was associated with being in a non-responding trajectory group. Our analysis cannot clarify whether a longer course of illness is a marker of or causative factor involved in treatment resistance. We also found that better list recognition performance (a sensitive measure of learning among older adults) was associated with having a rapid response.

Patients with more chronic and severe LLD are likely burdened with a greater level of specific cerebral vascular abnormalities [225]. These markers of brain pathology have been previously linked to treatment resistance [226-228]. Perhaps emerging through prolonged episodes or other underlying resistance factors, atrophy and/or demyelination of specific neural circuits may cause treatment resistance. Our finding that higher list recognition scores were associated with a rapid response may indicate that relative preservation of hippocampal structures and functions, despite older age and depression, may facilitate recovery. On the other hand, brain pathology disrupting the neural circuits involved in guilt may mark difficult to treat depression. The specific neural circuits underlying variability and interconnections between symptom expression, cognitive function, and treatment response have not yet been isolated.

Strengths of our study include the novel data-driven profiling of pharmacological treatment response in the largest open-label trial for LLD conducted to date. Additional strengths include the comprehensive examination of previously established prognostic response factors including specific neuropsychological test performance plus the novel inclusion of individual depressive symptoms. We found that heterogeneity in symptom expression and cognitive co-morbidity might reflect differences in MDD phenotype, rooted in to-be-determined neurobiological substrates relevant to pharmacological response. The substantial possibility of confounding due to a lack of adequate pharmacological care was excluded by providing treatment appropriately (including sufficient monitoring, depression management support, as

well as careful dose titration). Even in this specialty care setting, patients with severe symptoms at baseline often failed to recover, and this finding highlights the importance of establishing a mechanistic understanding of treatment resistance.

Several limitations should be noted. The sample consisted of older adult out-patients and cannot necessarily be generalized to middle-aged/younger patients or older in-patients. Although providing adequate care minimized potential confounding (for example due to insufficient dosing), rates and patterns of response cannot necessarily be generalized to primary care settings where specialist monitoring may be minimal or absent. Reduced sleep was associated with trajectory grouping, however our reliance on self-report limits the specificity of this finding. Distinct patterns of overall response were examined, but influence of early change in specific symptoms was not. Analyses were prognostic and could not determine factors which, if any, moderate intervention efficacy. We did not account for unmeasured confounding potentially including genetic and social contextual factors. Our approach illustrates the important difference between “response rates” and “rates of response,” however we did not directly assess associations of prognostic factors with the rate of symptom change over time.

The biological mechanisms underlying the identified prognostic associations remain unknown and, in addition, our analysis cannot distinguish treatment resistance factors from downstream insults accumulated through a chronic depression course. Consistent associations of episode duration with resistance highlights the potential importance of treating depression early on; further, this consistent finding highlights challenge of isolating causal factors from downstream consequences. Mounting evidence of associations between specific cognitive deficits and treatment resistance calls for integrative studies of clinical/neuropsychological and brain structural factors in relation to LLD treatment response.

In sum, we found that longer episode duration, greater symptom burden with a relative lack of sleep deficits, great feelings of guilt, and lower list recognition scores were related to slower or absent treatment responses. When faced with a patient presenting with severe, longstanding depression with these co-morbidities, alternative treatment strategies or intensive short term-monitoring should be implemented. Although this recommendation is supported by the prognostic factors associated with distinct response patterns, mechanisms linking high levels of depression severity plus these clinical markers to treatment response are still unclear. Associations and interactions between clinical prognostic factors and biological markers have not yet been examined in the context of LLD treatment.

Future research integrating clinical and biological prognostic factors will increase our understanding of the mechanisms which determine treatment response trajectories. Such integration can support predictive analyses aimed at creating clinically accessible treatment allocation strategies. A major research priority is isolating the psychological and neurobiological circuits whose dysfunction causes treatment resistance. Such research can improve early detection strategies, decrease time to remission, and inform targeted prevention strategies to reduce the incidence of treatment resistant depression.

4.5 TABLES AND FIGURES

Table 23. BIC by number of groups for models with all linear exponents, and associated BIC log Bayes factor approximation

Number of Groups	BIC	2*ΔBIC (Evidence against H_o)
1	-11971.12	
2	-11243.70	1454.84
3	-11058.70	370
4	-10978.19	161.02
5	-10931.47	93.44
6	**-10888.79**	85.36
7*	-10883.20	11.18

*=included a small (<5%) trajectory group

Table 24. Posterior probabilities and odds of correct classification per trajectory group

	% (n)	Mean	SD	Min	Max	OCC
Rapid Response	15.23 (69)	0.90	0.14	0.51	0.99	57.67
Mod., Response	23.84 (108)	0.86	0.16	0.39	0.99	18.93
High, Response	5.52 (25)	0.88	0.16	0.51	0.99	128.47
Mod., Mixed/Non-response	19.43 (88)	0.84	0.17	0.35	0.99	20.49
High, Non-response 1	24.28 (110)	0.87	0.17	0.42	0.99	20.18
High, Non-response 2	11.70 (53)	0.90	0.16	0.40	1.00	70.65

Abbreviation: Mod.=Moderate

Table 25. Descriptive Patient Characteristics by Trajectory Group

	Rapid Response	Mod., Response	High, Response	Mod., Mixed/Non-response	High, Non-response 1	High, Non-response 2	p
Demographic factors							
White, % (n)	88.41 (61)	88.89 (96)	84 (21)	89.77 (79)	82.73 (91)	96.23 (51)	0.9902
Female % (n)	69.57 (48)	67.59 (73)	76 (19)	65.91 (58)	60.91 (67)	58.49 (31)	0.5046
Age	**70.13 (8.37)**	**70.81 (8.04)**	**67.73 (5.40)**	**69.45 (7.09)**	**67.44 (5.92)**	**67.41 (6.43)**	**0.0079**
BMI	29.76 (6.54)	29.48 (7.02)	29.17 (6.34)	29.78 (5.92)	30.94 (7.38)	29.86 (7.61)	0.6666
Education (years)	14.49 (3.16)	14.71 (2.88)	13.88 (2.85)	14.82 (2.91)	13.91 (2.33)	14.26 (2.97)	0.1826
Potential Prognostic Factors							
Age at first episode	**47.48 (20.67)**	**45.02 (22.15)**	**35.28 (20.57)**	**42.97 (21.63)**	**38.88 (21.02)**	**37.13 (21.39)**	**0.0183**
Episode duration (weeks)*	**239.55 (538.94)**	**224.66 (504.58)**	**130.84 (118.64)**	**327.28 (614.73)**	**410 (794.55)**	**292.5 (625.18)**	**0.0288**
Recurrent depression, % (n)	72.46 (50)	70.37 (76)	84 (21)	68.18 (60)	68.18 (75)	79.25 (42)	0.4751
Adequate prior treatment (ATHF=> 3), % (n)	60.87 (42)	52.78 (57)	48 (12)	59.77 (52)	66.67 (72)	81.13 (43)	**0.0164**
Number of drinks/week*	1.19 (2.96)	0.70 (1.58)	0.20 (0.65)	0.85 (1.80)	0.93 (2.67)	1.23 (3.23)	0.6912
SF-36 Physical Health	**45.40 (10.84)**	**43.18 (10.9)**	**43.53 (10.57)**	**43.57 (12.09)**	**40.98 (12.14)**	**38.67 (11.69)**	**0.0526**
CIRS Count**	5.62 (2.23)	6.44 (2.54)	6.04 (2.01)	6.13 (2.21)	6.26 (2.44)	5.94 (2.37)	0.4721
CIRS Total**	8.94 (4.68)	10.13 (4.58)	9.56 (3.85)	9.93 (3.96)	10.09 (4.62)	9.62 (4.65)	0.7146
SIS Total	1.83 (4.24)	1.76 (3.74)	1.28 (2.64)	2.38 (4.63)	2.38 (4.32)	3.94 (5.68)	0.0965
BSI Anxiety	**1.18 (0.85)**	**1.36 (0.89)**	**1.97 (0.92)**	**1.26 (0.82)**	**1.59 (0.94)**	**2.07 (0.91)**	**<0.0001**
Total Depression Scores							
Total baseline MADRS	**21.09 (4.12)**	**25.87 (4.84)**	**32.16 (4.06)**	**24.09 (4.22)**	**28.86 (4.64)**	**32.96 (4.11)**	**<0.0001**
Total 12 week MADRS	3.92 (5.59)	5.63 (4.26)	6.35 (4.05)	13.49 (6.63)	23.05 (4.67)	30.84 (4.86)	<0.0001

Mean (SD) shown unless otherwise noted; *p value shown after log transformation (mean and SD are not transformed); **BOLD** indicates selected prognostic factors; Abbreviation: Mod.=Moderate

Table 26. Bivariate associations between neuropsychological predictors and trajectory group

	Rapid Response	Mod., Response	High, Response	Mod., Mixed/Non-response	High, Non-response 1	High, Non-response 2
RBNAS						
Total	**1.03 (1.00-1.05)**	Ref	1.02 (0.98-1.05)	1.00 (0.98-1.02)	1.00 (0.98-1.03)	1.00 (0.98-1.03)
Visuospatial	1.02 (1.00-1.04)	Ref	1.01 (0.98-1.04)	1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.02 (1.00-1.04)
Attention	1.02 (1.00-1.04)	Ref	1.00 (0.97-1.03)	1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.00 (0.97-1.02)
Delayed	**1.03 (1.01-1.06)**	Ref	1.01 (0.98-1.04)	1.00 (0.98-1.03)	1.00 (0.98-1.02)	0.99 (0.97-1.01)
Immediate	1.02 (1.00-1.04)	Ref	1.02 (0.99-1.05)	1.00 (0.98-1.02)	1.00 (0.98-1.01)	1.01 (0.98-1.03)
Language	1.00 (0.97-1.03)	Ref	0.99 (0.95-1.03)	**0.97 (0.94-0.99)**	**0.97 (0.95-1.00)**	**0.96 (0.93-0.99)**
D-KEFS						
Stroop C-W (CWI3CSSFinal)	1.05 (0.94-1.17)	Ref	1.15 (0.98-1.36)	1.04 (0.94-1.16)	1.04 (0.94-1.16)	1.02 (0.90-1.15)
Trails 4 v 5	1.01 (0.92-1.10)	Ref	0.96 (0.84-1.10)	0.98 (0.89-1.07)	0.97 (0.89-1.06)	0.97 (0.87-1.08)

Bold indicates significant ($p<0.05$) association

Table 27. Multivariable model predicting trajectory group

	Rapid Response	Mod., Response	High, Response	Mod., Mixed/Non-response	High, Non-response 1	High, Non-response 2
Age	1.01 (0.95-1.09)	Ref	0.96 (0.88-1.04)	1.02 (0.96-1.08)	0.96 (0.91-1.02)	0.98 (0.90-1.07)
Education	0.83 (0.68-1.01)	Ref	0.89 (0.73-1.08)	0.91 (0.78-1.07)	**0.87 (0.76-0.99)**	0.93 (0.77-1.12)
Baseline MADRS	**0.56 (0.46-0.69)**	Ref	**1.43 (1.21-1.69)**	**0.76 (0.65-0.88)**	**1.13 (1.00-1.27)**	**1.54 (1.30-1.83)**
Reduced Sleep	0.83 (0.59-1.17)	Ref	0.99 (0.62-1.59)	**0.72 (0.54-0.96)**	**0.69 (0.53-0.91)**	**0.62 (0.42-0.91)**
Work/activity impairment	1.29 (0.63-2.65)	Ref	1.68 (0.57-4.95)	1.51 (0.75-3.02)	0.97 (0.55-1.70)	**3.65 (1.22-10.99)**
Feelings of Guilt	0.62 (0.32-1.19)		1.47 (0.81-2.69)	1.13 (0.67-1.90)	1.49 (0.99-2.25)	**2.16 (1.23-3.79)**
List Recognition	**2.22 (1.18-4.20)**	Ref	1.05 (0.62-1.77)	1.02 (0.68-1.53)	0.99 (0.70-1.42)	0.67 (0.43-1.05)
Adequate prior Rx	2.12 (0.73-6.16)	Ref	0.34 (0.11-1.07)	2.06 (0.84-5.04)	1.84 (0.86-3.90)	2.81 (0.89-8.90)
Episode duration (log)	1.11 (0.78-1.60)	Ref	1.25 (0.84-1.86)	**1.40 (1.04-1.87)**	**1.54 (1.20-1.96)**	1.32 (0.93-1.88)

Estimates were also adjusted for study site; Bold indicates $p<0.05$

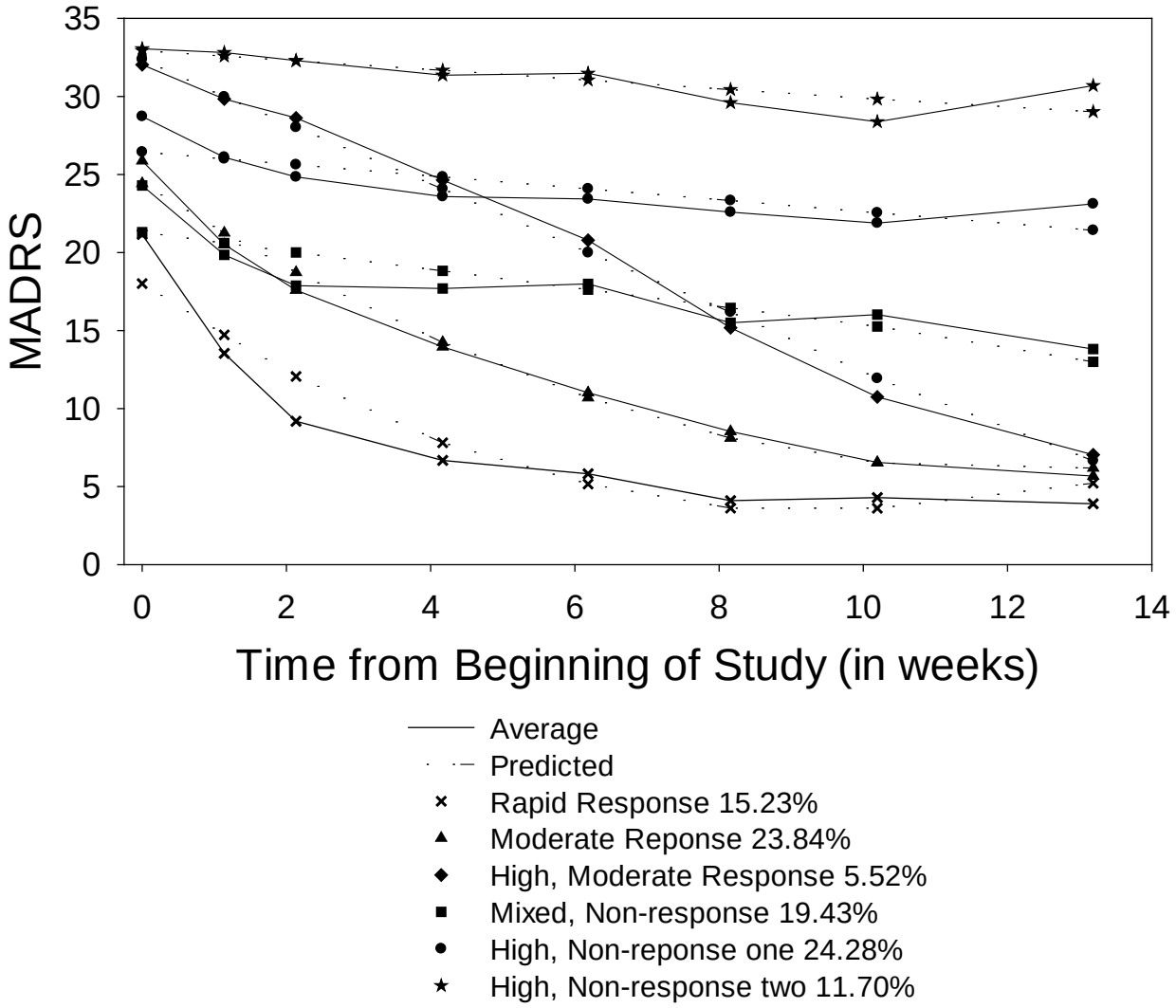

Figure 5. Data-derived trajectories of depressive symptom severity over 12-weeks of open-label treatment

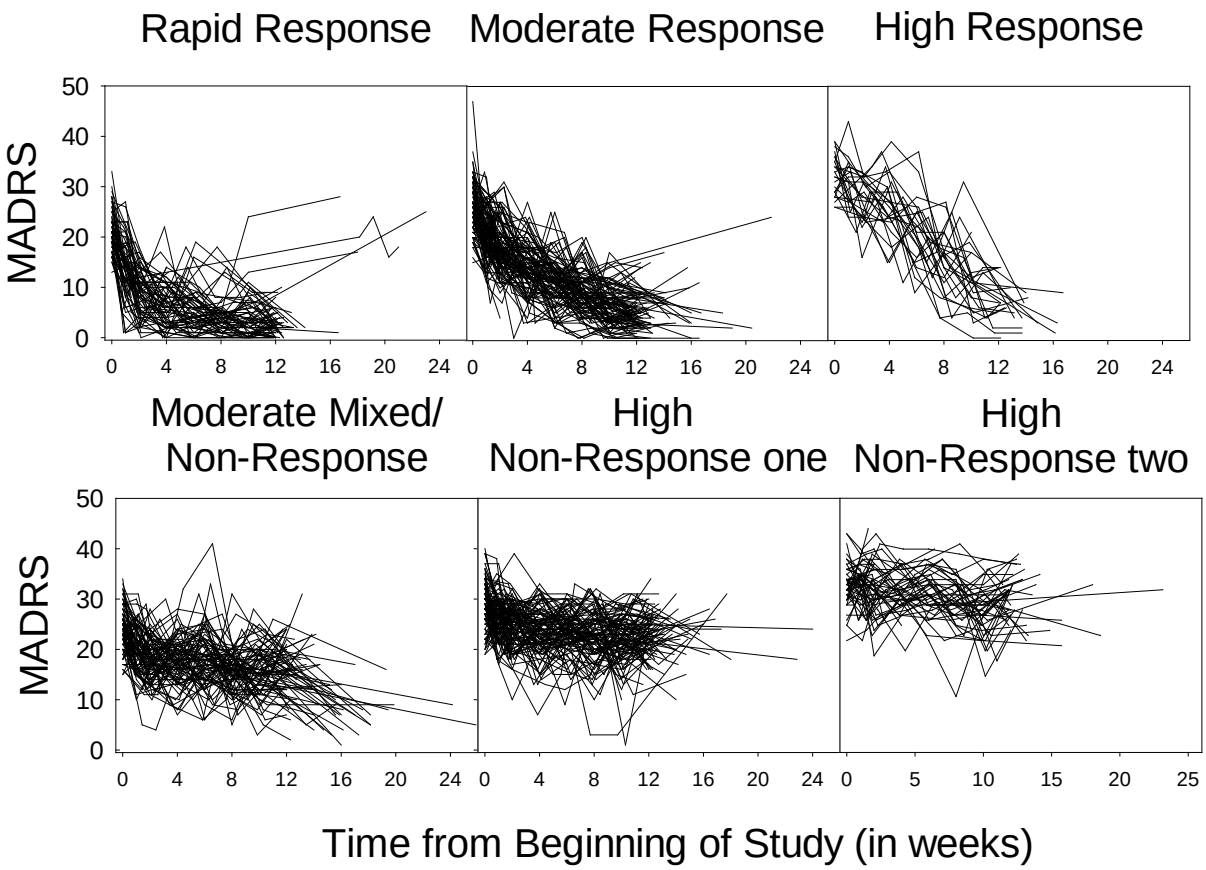

Figure 6. Spaghetti plots by trajectory group

5.0 PUBLIC HEALTH SIGNIFICANCE

Sub-diagnostic sleep and depressive syndromes are common among older adults. Specifically, we found a high prevalence of subjective sleep complaints (37.46% of the sample) and depressive syndromes characterized by somatic/apathy symptoms (32.44% of the sample). An important novel contribution of this work is the finding that a portion (5.74% of the sample) of men experiencing only somatic/apathy symptoms also reported impairment due to their emotional state; this finding highlights the importance of investigating the burden of sub-diagnostic syndromes among older adults. Since the important correlates of these syndromes were medication use and aspects of physical health, chronic disease prevention may reduce the overall burden of these syndromes on the aging population. Future longitudinal research is needed to understand the development and long term consequences of sub-diagnostic syndromes.

We found that baseline sleep or depressive syndromes were not related to future change in overall depression severity. However, we identified a novel behavioral marker of risk for future increases in depressive symptoms: having a delay in activity timing or having combined advanced/dampened/compressed activity rhythms were independently related to the development of depressive symptoms. Although we did not investigate the longitudinal determinants of these patterns of rest-activity rhythm disturbances, IADL impairment was related to being in these groups. Avoiding disability and maintaining appropriately timed activity may therefore prevent

the accumulation of depression symptoms in late-life. Intervention research should assess whether modifying these behavioral rhythms can prevent late-life depression.

Presently, however, prevention alone will not suffice to relieve the burden of depression for many older adults. Indeed, over 4% of the men in the MrOS Sleep Study appeared depressed and were characterized by a high probability of endorsing a range of psychological, cognitive, somatic, and apathy symptoms along with impairment. For individuals with this or similar symptom patterns and severity, tertiary intervention (treatment) is needed. But in a large sample of older adults treated with first-line pharmacological care in a specialty setting, we found that 55% experienced a poor treatment response trajectory. Having more severe depression at treatment baseline was often associated with treatment resistance; however, we also found that high baseline severity was neither necessary nor sufficient in conferring treatment resistance. Specific cognitive performance deficits (list recognition/learning) and symptom expression may contribute to treatment resistance; future work is needed to assimilate these findings with biological data. Valid clinical tools which detect treatment resistance at patient intake can decrease the time to remission, save clinical effort, and eliminate patient suffering.

In conclusion, the burden of late-life depression is both substantial and heterogeneous. But opportunities for prevention and treatment innovation abound. Specific physical health and behavioral factors are linked to depression development; reducing the prevalence of these factors (i.e. diabetes, IADL impairments, falls, and specific patterns of rest and activity) may attenuate the burden of late-life depression. Prolonged episode duration is related to a less favorable treatment response trajectory, suggesting that when prevention fails, intervening early may be crucial. In a rapidly aging world, understanding the mechanisms involved in the pathogenesis and resolution of late-life depression is a major public health priority.

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