From Department of Neurobiology, Care Sciences and Society
Karolinska Institutet, Stockholm, Sweden

Factors associated with Behavioral and Psychological Symptoms of Dementia

Emilia Schwertner

Karolinska Institutet

Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-449-8
Cover illustration: To jest pipidówka w sierpniu" by Marian Siwek. Used with permission from Iwona Siwek-Front

Factors associated with Behavioral and Psychological Symptoms of Dementia
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Emilia Schwertner

The thesis will be defended in public at room DNA, floor 5 at NEO building, Huddinge, January 21th, 2022 at 9.00 am

Principal Supervisor:
Professor Dorota Religa
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Division of Clinical Geriatrics

Co-supervisor(s):
Associate Professor Katarina Nägga
Linköping University
Department of Health, Medicine and Caring Sciences
Division of Prevention, Rehabilitation and Community Medicine

Associate Professor. Joana B. Pereira
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Division of Clinical Geriatrics

Professor Maria Eriksdotter
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Division of Clinical Geriatrics

Professor Bengt Winblad
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Division of Neurogeriatrics

Opponent:
Professor Geir Selbæk
University of Oslo
Department of Geriatric Medicine

Examination Board:
Associate Professor Karin Modig
Karolinska Institutet
Department of Environmental Medicine

Professor Börje Bjelke
University of Oslo
Division of Medicine and Laboratory Sciences

Associate Professor Marc Guitart-Masip
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Aging research center

Dedicated to patients and their families and caregivers.

POPULAR SCIENCE SUMMARY OF THE THESIS

In an aging society such as Sweden, legislators will face more and more challenges regarding treatment of individuals with dementia. Caring for persons suffering from dementia poses various ethical challenges about how to find balance between their autonomy, well-being, and safety. Additionally, the caregiver will sometimes have to face difficult decisions regarding the proper therapy for non-cognitive symptoms that almost all individuals with dementia experience during the course of their illness.

This Thesis covers the subject of Behavioral and psychological symptoms of dementia (BPSD). BPSD refers to all non-cognitive symptoms of dementia, such as psychotic and affective symptoms, hyperactivity, and apathy. The first study describes BPSD in various dementia diagnoses, whereas the second study focuses on the link between unmet needs and BPSD. The first two studies included only individuals residing in long-term care facilities. In Study 3, the risk of death associated with antipsychotic treatment was investigated. Study 4, on the other hand, concerns an issue that has not received much attention, especially among European researchers. More specifically, we used the Swedish Register for Cognitive Disorders / Dementia (SveDem) to describe firearm ownership in individuals with dementia in Sweden and investigate which of the registered characteristics of the person were considered by doctors when they reported the person as unfit to have a firearm.

In summary, we found that BPSD is common in individuals with dementia residing in long-term care facilities, in particular aberrant motor behavior, agitation/aggression and irritability. Additionally, we observed that individuals with dementia may have several of their needs unmet, the most common of which were pain, sleeping problems, impaired hearing and vision. Importantly, there was a relationship between the number of unmet needs and BPSD in each type of dementia. We also found that individuals with dementia are administered both typical and atypical antipsychotics. Their use was associated with a higher risk of death. In our cohort, 3.4% of individuals owned a firearm. Owners of firearms were typically younger males who were still living more independent lives. The decision to remove the firearm was not decided just on the premise of a dementia diagnosis, but rather on the basis of a number of factors, such as type of dementia diagnosis, sex, level of cognitive impairment, psychiatric medication, and living arrangements.

ABSTRACT

Most people with dementia suffer behavioral and psychological symptoms (BPSD). These symptoms add to caregiver stress and accelerate cognitive decline. The etiology of BPSD is complex, with multiple factors influencing symptom manifestation. The ability to accommodate and communicate needs decreases with cognitive deterioration. Unmet needs may explain why some individuals, despite having the same diagnosis and degree of cognitive impairment, have more severe BPSD. BPSD is treated with both atypical and typical antipsychotics (APD). Numerous studies demonstrated that APD treatment in individuals with dementia might cause major side effects, including death. The purpose of this Thesis is to examine factors associated with BPSD in a large group of individuals with dementia.

The Thesis covers four cross-sectional investigations using data from five Swedish registries: The Swedish registry for cognitive/dementia disorders (SveDem), the Swedish Behavioral and psychological symptoms of dementia Registry (BPSD registry), the Swedish Prescribed Drug Registry (SPDR), the Swedish Cause of Death Registry (CODR), and the Swedish National Patient Registry (NPR). Six types of diagnoses were included in the studies: Alzheimer's disease (AD), vascular dementia (VaD), mixed (Mixed) dementia, Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD) and unspecified dementia (UNS).

In **Study 1**, we discovered that 75% of individuals with dementia exhibited at least one clinically significant BPSD, the most prevalent being aberrant motor behavior, agitation/aggression and irritability. In comparison to AD, we found a lower risk of delusions (in FTD, UNS), hallucinations (FTD), agitation (VaD, PDD, UNS), elation/euphoria (DLB), anxiety (Mixed, VaD, unspecified dementia), disinhibition (in PDD); irritability (in DLB, FTD, UNS), aberrant motor behavior (Mixed, VaD, UNS), sleep and night-time behavior changes (UNS). Higher risk of delusions (DLB), hallucinations (DLB, PDD), apathy (VaD, FTD), disinhibition (FTD) and appetite and eating abnormalities (FTD) were also found in comparison to AD. In **Study 2**, pain was the most prevalent unmet need, followed by sleeping disturbances, impaired hearing and impaired vision. Additionally, we found that the risk of BPSD increases with unmet physical or psychological needs in dementia. In **Study 3**, APD use at the time of dementia diagnosis was associated with increased mortality risk across the cohort and by dementia subtype. In **Study 4**, we found that out of 53,384 individuals with dementia, 1,823 owned a firearm and 419 were unfit owners. Owners of firearms were mostly male, younger, living alone and without homecare support. Living with another person, frontotemporal dementia, APD and hypnotics prescription, being diagnosed in a memory/cognitive clinic, female gender, and mild and moderate dementia were the most important predictors of being reported to the police.

In conclusion, individuals with dementia who live in long-term care facilities frequently develop BPSD. Additionally, unmet needs are significantly associated with BPSD in each dementia type. Individuals with dementia receive both typical and atypical APDs, however, their use is associated with an increased risk of death. Finally, we found that the decision to withdraw the firearm is based on a variety of clinical factors associated with dementia.

LIST OF SCIENTIFIC PAPERS

I. **Schwertner E**, Secnik J, Garcia-Ptacek S, Johansson B, Nagga K, Eriksdotter M,Winblad B, Religa D. Antipsychotic Treatment Associated With Increased Mortality Risk in Patients With Dementia. A Registry-Based Observational Cohort Study. J Am Med Dir Assoc. 2019 Mar;20(3):323-329.e2. doi: 10.1016/j.jamda.2018.12.019. PMID: 30824220.

II. **Schwertner E**, Zelic R, Secnik J, Johansson B, Winblad B, Eriksdotter M, Religa D. Biting the Bullet: Firearm Ownership in Persons with Dementia. A Registry-Based Observational Study. J Alzheimers Dis. 2021;81(1):179-188. doi:10.3233/JAD-201365. PMID: 33720891; PMCID: PMC8203223.

III. **Schwertner E**, Pereira J, Xu H, Secnik J, Winblad B, Eriksdotter M, Nagga. K/Religa D. Behavioral and psychological symptoms of dementia in different dementia disorders: A large-scale study of 10 000 individuals. *Manuscript. Under review in J Alzheimers Dis*

IV. **Schwertner E**, Pereira J, Winblad B, Eriksdotter M, Religa D/Nagga. K. Relationship between unmet needs and behavioral and psychological symptoms of dementia in 10 000 individuals with dementia. *Manuscript.*

SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

I. Secnik J, Xu H, **Schwertner E**, Hammar N, Alvarsson M, Winblad B, Eriksdotter M, Garcia-Ptacek S, Religa D. The association of antidiabetic medications and Mini-Mental State Examination scores in patients with diabetes and dementia. Accepted for publication on 9.11.2021 in Alzheimer's Research & Therapy;

II. Muurling M, de Boer C, Kozak R, Religa D, Koychev I, Verheij H, Nies VJM, Duyndam A, Sood M, Fröhlich H, Hannesdottir K, Erdemli G, Lucivero F, LancasterC, Hinds C, Stravopoulos TG, Nikolopoulos S, Kompatsiaris I, Manyakov NV,Owens AP, Narayan VA, Aarsland D, Visser PJ; **RADAR-AD Consortium**. Remote monitoring technologies in Alzheimer's disease: design of the RADAR-AD study. Alzheimers Res Ther. 2021 Apr 23;13(1):89. doi: 10.1186/s13195-021-00825-4. PMID: 33892789;PMCID: PMC8063580.

III. Kalar I, Xu H, Secnik J, **Schwertner E**, Kramberger MG, Winblad B, von Euler M, Eriksdotter M, Garcia-Ptacek S. Calcium channel blockers, survival and ischaemic stroke in patients with dementia: a Swedish registry study. J Intern Med. 2021 Apr;289(4):508-522. doi: 10.1111/joim.13170. Epub 2020 Sep 14. PMID: 32854138; PMCID: PMC8049076.

IV. Secnik J, Xu H, **Schwertner E**, Hammar N, Alvarsson M, Winblad B, Eriksdotter M, Garcia-Ptacek S, Religa D. Dementia Diagnosis Is Associated with Changes in Antidiabetic Drug Prescription: An Open-Cohort Study of ~130,000 Swedish Subjects over 14 Years. J Alzheimers Dis. 2020;76(4):1581-1594. doi:10.3233/JAD-200618. PMID: 32741836; PMCID: PMC7504989.

V. Secnik J, **Schwertner E**, Alvarsson M, Hammar N, Fastbom J, Winblad B, Garcia-Ptacek S, Religa D, Eriksdotter M. Cholinesterase inhibitors in patients with diabetes mellitus and dementia: an open-cohort study of ~23 000 patients from the Swedish Dementia Registry. BMJ Open Diabetes Res Care. 2020 Jan;8(1):e000833. doi: 10.1136/bmjdrc-2019-000833. PMID: 31958305; PMCID:PMC7039592.

VI. Pilarczyk J, **Schwertner E,** Wołoszyn K, Kuniecki M. Phase of the menstrual cycle affects engagement of attention with emotional images.Psychoneuroendocrinology. 2019 Jun;104:25-32. doi:10.1016/j.psyneuen.2019.02.009. Epub 2019 Feb 12. PMID: 30784902.

VII. Magierski R, Sobow T, **Schwertner E**, Religa D. Pharmacotherapy of Behavioral and Psychological Symptoms of Dementia: State of the Art and Future Progress.Front Pharmacol. 2020 Jul 31;11:1168. doi: 10.3389/fphar.2020.01168. PMID:32848775; PMCID: PMC7413102.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
APD	Antipsychotics
ATC	Anatomical Therapeutic Chemical
AUC	Area under the receiver operating characteristic curve
BPSD	Behavioral and psychological symptoms of dementia
ChEI	Cholinesterase inhibitors
CODR	Swedish Cause of Death Register
CCI	Charlson Comorbidity Index
CI	Confidence intervals
DA	Dominance analyses
DLB	Dementia with Lewy bodies
FFT	Five Factor-theory
FTD	Frontotemporal dementia
HDRS	Hamilton Depression Rating Scale
HR	Hazard ratio
IPA	International Psychiatric Association
LBD	Lewy body dementia
MCI	Mild cognitive impairment
NFT	Neurofibrillary tangles
Mixed	Mixed-pathology dementia
MMSE	Mini-Mental State Examination
NPI	The Neuropsychiatric Inventory
NPR	Swedish National Patient Register
NPT	Non-pharmacological treatment
OR	Odds ratio
SPDR	Swedish Prescribed Drug Register
SSRIs	Selective serotonin reuptake inhibitors
SveDem	The Swedish registry for cognitive/dementia disorders
UNS	Unspecified dementia
VaD	Vascular dementia

VRA	Violent risk assessment

1 INTRODUCTION

Dementia is a syndrome that can be caused by several etiologies with the Alzheimer's Disease (AD) being the most common form of dementia. Cognitive impairment is considered the hallmark of dementia, however, in addition to it all individuals with dementia will experience at least one behavioral and psychological symptom of dementia (BPSD) in the course of the disease.[1]

Although BPSD has been somewhat neglected in dementia research, it was identified as an integral component of dementia disorders even in the earliest accounts of dementia. In his classic early-twentieth-century case report of the disease, Alois Alzheimer recognized behavioral abnormalities as prominent manifestations in his case description.[2] Paranoia, sleep disorders, aggressiveness, crying, and progressive confusion accompanied disturbances of memory of the first AD patient.[3] However, only in the 1980s did BPSD become an important subject of clinical and scientific discussion. Finally, it was in 1999 when the term BPSD was introduced by the International Psychiatric Association (IPA) replacing the former term "behavioral disturbances".[4] IPA adopted the general definition of BPSD operationalizing them as "symptoms of disturbed perception, thought content, mood, or behavior that frequently occur in patients with dementia."[5] BPSD are widespread in all subtypes of dementia but typically differ in the frequency and severity of individual symptoms in individuals with different diagnoses of dementia.[6] Although many studies have reported the presence of these symptoms in dementia, they reported inconclusive findings. Additionally, their conclusive description is complicated by the complex etiology of BPSD and the tendency of some of BPSD to fluctuate in time, while other remaining relatively stable.[7,8]

Nowadays, BPSD are studied and commonly found with similar prevalence across different continents around the world in countries such as Australia,[9] Central African Republic and Republic of Congo,[10] Chile,[11] China,[12] Hungary,[13] Norway,[14] Taiwan,[15] Tanzania,[16] the Netherlands,[17] the United States,[18] among others. The widespread presence and high prevalence of BPSD is a matter of concern. These symptoms have been identified as a major contributor to the burden of both patients and their caregivers, moving to long-term care facilities, higher morbidity and greater rates of mortality.[6] Care for relatives with BPSD is associated with reduced quality of life, poorer health and lower income from work.[19,20] Finally, BPSD also play an important role in ethical dilemmas related to management of behavior of individuals with dementia. In order to ensure safety of individuals with dementia and their

environments, caregivers will have to assess the potential risk that the behavior can cause and implement appropriate prevention and treatment. For these reasons, in the past few years, there has been an increasing worldwide effort to place BPSD in a more central position in the dementia research and care.[4]

2 LITERATURE REVIEW

2.1 ASSESSMENT OF BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

A number of tools to assess BPSD has been growing with eighty-three instruments identified by 2014.[21] Currently, the Neuropsychiatric Inventory (NPI) is the most common tool to assess BPSD.[22] It was developed in 1994 by Cummings et al.[23] Even though it was originally meant to target individuals with dementia, it is currently also used to examine individuals with psychotic, affective, and other neurological illnesses, including Parkinson's disease and epilepsy. The NPI has been translated into a variety of languages, such as Chinese, Danish, Dutch, French, German, Greek, Hebrew, Italian, Japanese, Norwegian, Portuguese, Spanish, Swedish, and Thai.

Prior to the NPI, neuropsychiatric research in dementia mostly relied on techniques designed for mental diseases including schizophrenia and major depressive disorder.[24] However, symptoms observed in dementia differed from a presentation of psychiatric disorders, necessitating the development of a tool specific for this group of individuals. For example, the Hamilton Depression Rating Scale (HDRS), which is used to evaluate mood changes in major depressive disorder, includes features of depression such as withdrawal, appetite changes, and sleep disturbances that may occur in dementia without depression. In contrast, the depression/dysphoria domain of the NPI only covers mood-related items, while apathy, sleep changes, and appetite changes are separate items of NPI.

When it was initially created, NPI evaluated ten behavioral disorders: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor behavior. The measure was then modified and expanded to 12 categories, including night-time behavior disturbances as well as appetite and eating abnormalities. The NPI is a quantitative measure in a form of a semi-structured interview with a caregiver. According to Cummings et al., caregivers are the most optimal informants of the behavior of the person with dementia, since this group of individuals is deemed unable to recall or explain their symptom themselves.[23]

The NPI evaluates not only the presence of each behavior, but also its frequency and severity. The frequency of symptoms is scored on a four-point scale from 1 to 4 (1: occasionally, 2: less than once a week, 3: very frequently, 4: more than once a day) and the severity of the behavior is rated on a three-point scale (1: mild, 2: moderate, or 3: severe). Additionally, caregivers are asked to assess the distress associated with caring for an individual with a given symptom on a 6-point scale (0: not at all distressing, 1: minimally distressing, 2: mildly distressing, 3: moderately distressing, 4:severely distressing and 5: very severely or extremely distressing).

Despite being a frequently used and valuable tool, NPI is not without limitations.[25] First of all, Cummings et al., did not provide a conceptual framework behind the NPI.[23] Symptoms were chosen based on the extensive literature review and then categorized into domains. Although it is not stated explicitly, NPI seems to reflect the biomedical perspective in the approach to diseases, that is the disease causes symptoms, hence an assessment of the symptoms' response to therapy is required. This also implies that NPI does not place so much importance on the significance of the symptoms but only quantifies them. This offers both advantages and disadvantages. There is no attempt to identify if behaviors are caused by the physical or social environment, other unmet needs or medical reasons. For this reason, it does not encourage reflection about the underlying reasons of the behavior and may result in detection biases when behaviors are indiscriminately attributed to BPSD. However, the instrument is easy and quick to administer which is important in clinical settings.

Second, the NPI does not seek to understand the perspective of the individuals with dementia themselves in assessing their symptom. Failing to include the perspective of persons whose behavior is a matter of observations risks not only clinical problems but is also ethically concerning. For example, McKinlay et al. compared caregiver and self-reports about BPSD using the NPI.[26] Although both patients and caregivers reported similar rates of symptoms, the researchers found that there was little agreement amongst the dyads. The authors speculated that the lack of agreement may be due to caregivers being asked to report on issues that were not immediately apparent based on observed behavior and concluded that caregiver and patient reports cannot be considered interchangeable. Additionally, another study indicated that it is easy for unskilled nursing personnel to mistake certain anxiety symptoms for agitation.[27]

2.2 ETIOLOGY OF BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)

2.2.1 Models of Behavioral and psychological symptoms of dementia (BPSD)

An integral challenge in developing a unifying framework for BPSD is its heterogeneous presentation and etiology. Although BPSD primarily results from pathophysiological changes in the brain, neurodegeneration only explains part of its manifestation. BPSD is a complex phenomenon involving also other factors, such as comorbidity, characteristic of the environment and individual personality traits. Currently, there are few prevailing theoretical frameworks of BPSD – the unmet needs models, the need-driven, dementia-compromised behavior model, the behavioural/learning model and the environmental vulnerability/reduced stress-threshold models.[28]

Unmet needs model

Unmet needs model focuses on the relationship between unmet needs and the relationship with BPSD. Unmet needs are defined as the needs that are not readily evident to the observer or caregiver, or that caregivers do not feel they are capable of meeting.[29] According to the unmet needs model cognitive decline impairs the one's ability to meet one's requirements as communication becomes more difficult, as well as the one's ability to provide for oneself.[29,30] In this perspective, BPSD result from a combination of lifelong habits, personality, current physical and mental states with not optimal environmental conditions. For example, in this model agitation could have a compensatory function (alleviation of boredom) as well as communicatory - to communicate the need to a caregiver.

The need-driven, dementia-compromised behavior model

According to the need-driven, dementia-compromised behavior model,[31,32] BPSD is caused by the caregiver's failure to comprehend needs and the incapacity of the individual with dementia to communicate those needs. Therefore, in this view, BPSD is a symptom of unmet needs. Furthermore, the model distinguishes between background factors and proximal factors that interacts to cause BPSD. Neurological, health, and psychosocial factors constitute relatively stable, background factors. On the other hand, proximal factors - current situational issues and events - are more susceptible to change and often directly antedate the BPSD. Proximal factors include variables within the person (e.g. pain, fatigue), physical environment (e.g. noise, room temperature), and social environment.

The behavioural/learning model

The 'behavioural/learning' model proposes that BPSD is formed through caregiver reinforcement (e.g. caregiver's attention) in the conditioning process.[28] This means, that a connection between antecedents, behavior, and reinforcement has been learned, and to change this connection, a different learning experience is needed. Antecedents-Behaviour-Consequences (A-B-C) approach to management of BPSD entails tracing antecedent factors to the expression of BPSD, and reviewing the consequences, which may unintentionally reward the person and thereby reinforce BPSD.

Environmental vulnerability/reduced stress-threshold model

Environmental model associates the occurrence of BPSD with the mismatch between the needs and abilities of the individuals with dementia and their environment. Progressive lower stress threshold model posits that individuals with dementia have a lowered stress threshold and thereby progressively lose their coping abilities. This leads them to perceive their environment as more and more stressful.[33] Environmental conditions optimal for a cognitively healthy person can therefore exceed ability of the individual with dementia to cope and adapt. Thus, intervention strategies based on this model focus on creating a less stressful environment by considering the individuality of the individual with dementia, focusing on their interaction with the environment, and adapting the environment to the reduced cognitive capacities of the individuals with dementia.

2.2.2 Kales and colleagues comprehensive model of BPSD

The various models of BPSD are not mutually exclusive. Due to the lower stress threshold, individual with dementia can be more susceptible to environmental antecedents and consequences. Additionally, the lower stress threshold may lead to unmet needs when normal levels of stimulation are interpreted as overstimulation. Further, individual symptoms may differ in their etiologies and the trajectories leading to symptoms vary between individuals with dementia. Kales and colleagues[34] proposed a comprehensive model explaining how different dementia-related factors increase the vulnerability to stressors and thereby disrupt the ability of patients to functionally interact with others, contributing to the occurrence of BPSD. These factors were categorized into those associated with: a) the patient (brain pathology, unmet needs, comorbidity and medication, premorbid personality), b) the environment (e.g. stimulation), and c) the caregiver (e.g. stress, coping strategies, perceived burden). Dementia, according to their model, may directly induce symptoms by altering brain circuitry involved in

behavior and emotion. Additionally, behaviors can be triggered by caregiver and environmental factors alone or in combination with the circuit abnormalities seen in brain degeneration.

Patient-related factors

Neurobiology. Neurobiological factors, according to the need-driven, dementia-compromised behavior model, are distant factors that interact with the environment resulting in BPSD. However, BPSD most likely cannot be linked to single-brain atrophy, dysfunctions or neurochemical alterations in the brain. Similar to other psychiatric disorders, symptoms may be associated with multiple and distributed foci of structural brain abnormalities. Additionally, the same set of networks may be impacted across many different symptoms in different subtypes of dementia**.** Several parallel brain and behavioral mechanisms have been identified to underlie single BPSD or spectrum of symptoms. Frontal-subcortical circuits responsible for planning, executive function, motivation, inhibitory control and conformity with social norms are subject to neurodegeneration in dementia and correlate with BPSD.[35,36] Additionally, imbalance of different neurotransmitters can contribute to the pathogenesis of behavioral abnormalities in dementia.[37] For instance, monoaminergic neurotransmitters diffusely project to almost all regions of the brain involved in the regulation of behavior.[37] Serotonin and dopamine have also been implicated in several BPSD.[38,39] The cholinergic system represents the most important neuromodulatory neurotransmitter system in the brain and cholinergic deficits have been shown to contribute to several of BPSD.[40]

Comorbidities. Individuals with dementia often may suffer from other medical problems or undetected diseases, with 66% of them having at least one undiagnosed disease.[41] For example, bacteriuria, hyperglycemia, and anemia have been found common in individuals with dementia.[42] Individuals with dementia are more likely than those without cognitive impairment to suffer from untreated medical conditions.[42,43] They may not be able to appropriately communicate their symptoms, especially at the moderate to severe disease stage, making the identification of medical concerns a significant treatment difficulty.[44,45] Treatment is further complicated by the unusual or asymptomatic presentation of diseases in elderly individuals, for example, the absence of pain in the presence of a disease that is known to produce pain, or lack of fever in the presence of a condition that is known to induce fever.[46] Pre-existing dementia can be an additional factor associated with atypical presentations of illnesses.[46] These conditions might lead to severe behavioral symptomatology if left untreated. From the perspective of the unmet need model of BPSD, individuals communicate their needs through behavior. Since the possibility of verbal report is limited, individuals may use their behavior as a channel of communication. Undetected diseases were shown to result in BPSD, including

agitation, repetitive questions, screams, delusions, hallucinations, depression[42] or aberrant eating behavior.[42,47] For example, pain and delirium can underlie sleeping abnormalities,[48] aggressive behavior,[49,50] eating problems, wandering, irritability, distress[51] and verbal/vocal behaviors.[30,51] In addition, drugs and their side effects can cause BPSD symptoms.[52–55] Antipsychotics can lead to confusion or somnolence, increased appetite, sedation and fatigue.[56,57] Selective serotonin reuptake inhibitors (SSRIs), a typical first-line therapy for depression, have been shown to induce apathy in older adults.[58] Caregivers may mistake behaviors as indicating the need for more psychotropic medication rather than determining whether there is an undiagnosed medical condition or other unmet need. As a result, many individuals with dementia may receive inadequate or even harmful treatment, for example restraining or psychotropic medication.

Personality. Despite the fact that numerous theories of personality have been developed, trait theory, has been the most widely used in studies exploring a link between personality and BPSD. Further, most of these studies involves a model that defines personality referring to Five Factor-theory (FFT). In FFT, traits are considered as basic tendencies that in combination with external influences can cause habitual patterns of behavior, thinking, and emotion.[59] Traits can be inferred from behaviors that cluster around five dimensions: openness, conscientiousness, extraversion, agreeability and neuroticism. According to this viewpoint, traits are relatively stable over time, differ between individuals (for example, some people are outgoing while others are not), are largely consistent across settings, and influence behavior.[60]

These dimensions are derived from a lexical method, which analyzes the natural-language terms people use to describe themselves and others.[61] According to the lexical hypothesis, most socially relevant and conspicuous psychological traits have become embedded in natural language. Therefore, the personality vocabulary of natural languages provides a wide, but finite, set of characteristics that individuals speaking that language have found essential and useful in their daily interactions.

Initially, researchers suggested that personality traits in persons over the age of 30 remained stable.[62] Recent research, however, has found a peak in trait consistency at the age of 50, as well as intraindividual shifts in personality trait trajectories.[63–65] Roberts et al. found that personality traits are malleable in old age.[66] More specifically, their meta-analysis revealed decreases in openness and extraversion and increases in agreeableness and conscientiousness.[66] These findings were partially corroborated by a longitudinal study that showed declines in neuroticism and extraversion but stability in openness, agreeableness, and conscientiousness.[67]

Long-term prospective studies suggested that in preclinical AD, there are no personality changes that are an early sign of the disease.[68] On the other hand, there are significant changes in personality with the beginning and progression of dementia, which are routinely observed by caregivers in retrospective study.[68] Differences in personality traits in mild cognitive impairment (MCI) and AD in comparison to the premorbid state or healthy aging include increased neuroticism as well as decreased extraversion, openness, conscientiousness, and agreeableness.[69,70]

Literature suggests that that of the five traits, neuroticism has the most associations with BPSD.[71–74] Associations have been found between neuroticism and mood and aggression-related symptoms, delusion, getting lost in familiar places, wandering off, being unable to be left alone, hallucinations, depression, periodic confusion, and an uncontrolled temper.[71–74] Regarding other traits, low premorbid agreeableness was associated with high levels of verbally aggressive behavior and high conscientiousness with less total BPSD, lower risk of getting lost in familiar places and higher independence and lower verbally nonaggressive behaviors.[73,74] Studies investigating the association between personality and BPSD in different subtypes of dementia are scarce. In AD, premorbid neuroticism was shown to be positively associated with depression[75–77] and anxiety,[78,79] and premorbid agreeableness was negatively related to agitation and irritability.[79] One study investigating premorbid personality traits in DLB found negative associations between openness and anxiety, agreeableness and delusion, as well as conscientiousness and agitation.[75]

The mechanisms underpinning the role of personality in developing individual BPSD are speculative. Personality shapes an individual's reactions to stress, health behaviors, and engagement in physical, cognitive, and social activities over the lifetime.[68] It is therefore possible that some of the behaviors and premorbid ways of being remain encoded in the ways the individual interacts with the surrounding environment after developing dementia.[80] Additionally, there may be some overlap in the brain structures and connectivity involved in personality traits and BPSD. For example, neuroticism was linked in previous studies to an altered connectivity between prefrontal cortex and amygdala.[81,82] These abnormalities may underly emotional reactivity common in individuals with high scores in neuroticism.[83] It has been suggested that neurodegenerative processes in dementia may enhance pre-existing vulnerability in neurotic individuals favoring the early emergence of affective and emotion dysregulation.[84]

Environmental factors

Physical environment design is becoming more widely acknowledged as a valuable tool in the treatment of individuals with AD and other dementias, particularly that many elements of the environment, such as noise levels, room lighting, appropriate crowding, and homelike design, are quite simple to modify. Competence and Environmental Press Model, also referred to as the Person–Environment Fit model illustrates people's interactions with their surroundings and stresses the impact of person–environment fit on person's emotions and behaviors.[85] Match between environmental demand and the individual's capability, results in positive emotions and adaptive behaviors. However, demands that surpass or fall below an individual's competency level may lead to maladaptive behaviors and negative emotions.

Due to the lower stress threshold in individuals with dementia, the correspondence between the individual's competence and the demands of the environment is particularly important in this population.[33] Physical environment can have a therapeutic effect on individuals with dementia, promoting well being and independence while also improving behavior and functionality.[86,87] On the other hand, malignant environment has been associated with dysregulation of behavior. For example, the number of staff in a unit in which an individual with dementia resides and its size can contribute to the occurrence of BPSD with , where facilities with more staff per patient are associated with less apathy.[88] Big unit size or nursing home size is related to BPSD, while small unit size for and homelike environment improved social abilities, functionality, and well-being.[9,87,89] Moreover, low social density is positively connected with residents' behavior and social abilities.[87] Another study indicated residents who had access to privacy were less anxious and aggressive.[90] Moreover, access to different types of common spaces with varying ambiance was associated with less social withdrawn and depression.[90] Further, bright light treatment has been shown to improve sleep, behavior and overall well-being.[87] There is considerable evidence linking excessive noise levels to undesirable behavior, whereas pleasant noises have been proven to be favorably stimulating.[91]

Caregiver factors and social interactions

The importance of positive social relationships in reaching psychological well-being cannot be overstated. Yet, it has been shown that the residents of long-term care facilities have little social contacts and spend significant amounts of time alone. It has been estimated that those with dementia spend up to 40% of their days doing nothing.[92] However, similar to the general population, the interactions the person with dementia have with the others as well the characteristics of caregivers have an impact on their quality life.

Caring for individuals with dementia is associated with an enormous burden with over 40% of family caregivers experiencing clinically significant depression or anxiety.[93–95] The burden of caring may be higher for older family caregivers, women, and if the person with dementia has more BPSDs.[94,95] The strongest correlations between the caregiver's burden and individual symptoms were found for delusions, followed by agitation/aggression, anxiety, irritability/lability, and dysphoria/depression.[96] Additionally, the way the caregivers deal with the burden of caring and their strategies for dealing with stress may further contribute to the development of BPSD. For example, a higher caregiver's burden and/or a lower quality of relationship contributes to the aggressive behavior.[50] The quality of the interaction also matters with activities that undermine a resident's preferences, goals, or status leading to more disrupted response from individuals with dementia. BPSD are also more likely to be observed when interactions are focused on task-centered care rather than person-centered care.[97] Persons with dementia react positively to interaction concerning their own preferences. If the conversation is more generic, the resident's attitude is negative, and associated with negative verbalizations.[92]

In line with this, studies found improved BPSD in individuals with dementia after caregiver-oriented interventions.[98,99] For example, after 12 months of care management, patients in the intervention group showed significant improvements in BPSD, and there was a significant reduction in caregiver stress compared to the control group. Furthermore, compared to the usual care group, there was no increase in the use of antipsychotics or sedative-hypnotic medicines in the intervention group.[98] Another intervention, consisting of three components - caregiver education, stress management and coping skills training - resulted in reductions in distress and depression and BPSD.[99] This is supported by recent meta-analyses summarizing caregiver oriented interventions, generally suggesting improvement of quality of life for persons with dementia and caregiver.[100,101]

2.3 BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS IN DIFFERENT DEMENTIA DIAGNOSES

2.3.1 Alzheimer disease (AD)

AD is the most common type of dementia and is associated with a progressive neuronal loss and cognitive impairment.[102] The main pathological features of AD are the accumulation of amyloid β (Aβ) into plaques and hyperphosphorylation of tau into neurofibrillary tangles (NFT).[102,103] The most frequent BPSD-symptoms observed in AD are apathy, followed by depression, aggression, anxiety and sleep disorder, while the least common was euphoria.[104] However, presentation of BPSD in AD may differ with respect to disease duration, age, study setting, education level and cognitive impairment.[104] A recent longitudinal study showed that occurrence of BPSD in AD can be grouped into three discernible phases with irritability, depression and sleep disturbances occurring in early phases, followed by apathy, anxiety, agitation, and appetite changes and finally delusions, hallucinations, and aberrant motor behavior.[105]

2.3.2 Vascular dementia (VaD)

VaD is a heterogeneous disease associated with ischaemic, hypoperfusive, or haemorrhagic brain lesions.[106] VaD can result from large-vessel disease, often associated with extensive cortical-subcortical damage, or due to small-artery disease and hypoperfusion, resulting in subcortical vascular disease.[106,107] Cerebrovascular lesions disrupt prefrontal-subcortical loops (e.g. nuclei of the basal ganglia and thalamus) and thereby underpin executive function impairment[108–110] and behavioral changes.[111–113] Although apathy seems to be the most common symptom in VaD,[114–116] individuals with VAD rank high also on depression, sleep disturbance,[117] irritability and agitation.[115] Moreover, the type of underlying vascular disease may be associated with different clinical profiles in VAD. Apathy, aberrant motor behavior, and hallucinations were shown to be more common in individuals with small-vessel VAD, whereas agitation and euphoria were more severe in those with large-vessel VAD.[115]

2.3.3 Dementia with Lewy Bodies (DLB)

The hallmark feature of DLB is the presence of numerous Lewy bodies composed of alpha-synuclein in the brainstem, subcortical nuclei, limbic cortex (cingulate, entorhinal, amygdala), and neocortex (temporal, frontal, parietal).[118] DLB is clinically characterized by the presence of dementia with deficits in attention, executive functions, visuo-spatial abilities but also memory impairment. The distinguishing features for the diagnosis of probable DLB are the

presence of fluctuating cognition, recurrent visual hallucinations and spontaneous motor features of Parkinsonism.[118] Psychotic symptoms are therefore the most prevalent symptoms in DLB, with delusions occurring in up to 80% of patients and hallucinations in up to 60% of DLB patients.[119] However, in addition to psychotic symptoms, a high prevalence of anxiety, depression, apathy, agitation, and sleep disorders have also been found.[120,121]

2.3.4 Frontotemporal dementia (FTD)

Clinical syndromes associated with frontotemporal lobar degeneration (FTLD) are characterized by progressive disintegration of the frontotemporal circuits and non-Alzheimer's disease type pathology.[122] The term FTD was introduced by the Lund&Manchester task force and refers specifically to the progressive behavioural syndrome.[123] Although other FTLD syndromes - semantic dementia (characterized by anomia and progressive loss of knowledge about words and objects) and progressive nonfluent aphasia (characterized by hesitant, nonfluent speech) - differ in their clinical characteristics in the early stages, they eventually develop symptoms characteristic for FTD.[124] Abnormal behavior is the core diagnostic feature of FTD.[123] Common symptoms in this group of patients include stereotypic behavior,[125–127] loss of personal and social awareness,[125,126] flattening of emotions, changes in appetite behavior (gluttony, food fads, sweet food preference), pacing, impaired insight, lack of pain awareness (however not so common), and hypersensitivity to neutral stimuli.[128,129]

2.4 MANAGEMENT OF BEHAVIORAL SYMPTOMS OF DEMENTIA

Caring for individuals with dementia raises ethical dilemmas of how to balance their autonomy and well-being, with their safety. With the increasing prevalence of dementia, public health workers will be challenged with new problems and some of them are particularly difficult because of their ethical aspects. When an individual has a diagnosis of dementia, decision making becomes somewhat of a grey area. What is more, persons diagnosed with dementia are part of the social environment and their behavior affects also their relatives and surrounding. For these reasons, it is important to be able to accurately predict the risk of potential violent behavior in these persons and subsequently take a decision about preventing and managing this behavior.

2.4.1 Violence risk assessment

Currently, there are no official guidelines for violent risk assessment (VRA) in individuals with dementia. Although there are instruments to measure potential violence in psychiatric patients

and healthy individuals, they may have little use in individuals with dementia. Older people are not often perpetrators of serious criminal offences, however, aggression is more common among individuals with dementia compared to a healthy population of the same age.[130–132] Cases of homicides involving patients with dementia have been described in the literature, mostly as a consequence of delusional believes associated with the victim (e.g. the imposter syndrome).[133–138] Furthermore, gradual impairment of executive functions[139,140] and visuospatial processing[141] can make it difficult for this group of individuals to handle firearm properly. Therefore, if the individuals with dementia have access to the firearm, they may cause unintentional injuries and deaths. Moreover, there are studies showing that individuals with dementia may have an increased risk of suicide,[142] particularly within the first three months after the dementia diagnosis.[143] In Sweden, people own firearm mostly for the purpose of hunting[144] and this carries an important social and personal meaning. For this reason, the decision about removing a firearm (analogously to losing a driving license) may lead to decrease of activity, social isolation and add to overall stigma associated with the diagnosis of dementia.[145] Additionally, the fear of having the firearm removed from patients' possession can discourage help seeking behavior and delay diagnosis.

2.4.2 Treatment of BPSD

Non-pharmacological treatments (NPT) of BPSD include behavioral, environmental and caring support interventions. Numerous guidelines recommend NPT as the first line strategy of support unless acute treatment is needed.[146] Although some of the interventions such as family caregiver interventions show higher efficacy than pharmacological treatment, there are numerous challenges in introducing them into standard care such as lack of training, time and reimbursement for implementation among others.[34] Research stresses the importance of developing strategies supporting caregiver-recipient relationship. Individuals with spousal carers decline more slowly.[147] Additionally, a close caregiver-recipient relationship had a comparable effect on cognitive decline to that seen with acetylcholinesterase inhibitors.[147,148]

Antipsychotics are still a commonly used treatments to alleviate aggression and psychosis.[149] However, their benefits may be observed only among those patients who tolerated the medications.[150] The use of atypical antipsychotics in dementia is controversial because of numerous studies showing that APD treatment may lead to serious side effects including death.[151] On the other hand, there are data suggesting that this association does not persist after adjusting for neuropsychiatric symptoms,[152] use of restraints or other factors like severity of dementia.[153,154] A novel antipsychotic, pimavanserin, showed promise in recent clinical trial.[155] The efficacy of pharmaceutical treatments for other BPSD is also still limited. Serotonergic

antidepressants are a popular treatment option for mood disorders, but a recent Cochrane meta-analysis found little evidence that they are beneficial in treating depression in individuals with dementia.[156] Pharmacotherapy of apathy includes cholinesterase inhibitors, memantine, antidepressants, APDs, and psychostimulants, however all have shown mixed or no success in treating apathy in Alzheimer's disease.[157–159] Melatonin, trazodone, benzodiazepines, Z-drugs (zolpidem, zopiclone, and zaleplon), and the ramelteon are all common sleep aids.[159] Other treatment possibilities include antihistaminergic drugs, herbal remedies, and antidepressants.[159] A Cochrane meta-analysis of the efficacy of pharmacotherapies for sleep disruptions in dementia found a scarcity of data on the subject.[160]

In Sweden, risperidone is the only antipsychotic recommended for short-term treatment (up to 6 weeks) of long-term aggression in individuals with dementia who harm themselves or others. Additionally, antidepressants (SSRI), benzodiazepines (oxazepam), hypnotics (clomethiazole) and memantine are used to manage the symptoms.[161,162] A recent study showed that these medications are regularly prescribed to individuals with dementia in Sweden.[163]

Questions have been raised about the ethics of these pharmacological approaches in the management of challenging behaviors. This is due to several reasons including whether it is ethical to give medication to people who are unable to give informed consent or even state their objection (e.g. drugs hidden in the food). Moreover, the association with caregiver workload suggest that pharmacotherapy may sometimes be prescribed for inappropriate reasons.[17,164]

3 RESEARCH AIMS

Overall aim

The overall aim of the thesis is to obtain a comprehensive understanding of different factors associated with treatment and mortality of individuals with Behavioral and psychological symptoms of Dementia (BPSD).

Specific aims

1. To characterize BPSD in individuals with different dementia diagnoses (Study 1).

2. To analyze the association between unmet needs and BPSD in individuals with different dementia diagnoses (Study 2).

3. To assess all-cause mortality of individuals with dementia treated with typical and atypical antipsychotic drugs (APDs) (Study 3).

4. To describe firearm ownership in individuals with dementia in Sweden and examine which characteristics are explaining physicians' decision to report a person to the police as unsuitable to possess a firearm (Study 4).

4 MATERIALS AND METHODS

The Thesis includes four cross-sectional observational studies based on data from five Swedish registries: The Swedish registry for cognitive/dementia disorders (SveDem), the Swedish Behavioral and psychological symptoms of dementia Registry (BPSD), the Swedish Prescribed Drug Registry (SPDR), the Swedish Cause of Death Registry (CODR), and the Swedish National Patient Registry (NPR). Individuals were identified and data was merged using a personal identity number (personnummer). Below is a brief description of the data sources, primary variable definitions, research samples, and statistical methods used.

4.1 THE SWEDISH REGISTRY FOR COGNITIVE/DEMENTIA DISORDERS (SVEDEM)

SveDem is a Swedish national quality-of-care registry that was formed in 2007 with the goal of registering all people in Sweden who have been diagnosed with dementia.[165] Individuals are enrolled to SveDem by their main care physician, a memory clinic, or nursing homes. SveDem now covers 78 percent of all primary care facilities, 100%of memory clinics, and 86 municipalities, with 97 570 unique patients registered.[166] The registry collects information on the patients' sociodemographic factors, such as age, gender, and living arrangements, as well as clinical (such as dementia type and severity, e.g., Mini-Mental State Examination (MMSE) scores)[167] and medicine prescriptions, e.g. antidementia, psychotropic and cardiovascular medication. Information is collected during baseline registration and at follow-ups (approximately annually).[165] Nine types of dementia diagnoses are registered in SveDem: early- and late-onset AD, Mixed, VaD, DLB, PDD, FTD, unspecified dementia (clinical examination to determine dementia type was not carried out or was difficult to specific the type) (UNS), and other dementia types (various dementia disorders, e.g. corticobasal degeneration, normal pressure hydrocephalus). Clinicians are instructed to use the 10th revision of the International Classification of Diseases (ICD-10). Additonally, the McKeith criteria are used for DLB,[168] the Lund-Manchester criteria for FTD[169] and the Movement Disorder Society Task Force criteria for PDD.[170] See Religa et al. for a more complete discussion of SveDem.[171]

4.2 THE SWEDISH BPSD REGISTRY

The Swedish BPSD registry was launched in 2010 with the goal of improving the quality of care for people with BPSD and achieving a nationwide standard of care across Sweden.[173] Until December 2019, a total of 73 585 individuals were registered in the BPSD registry. The estimated coverage of individuals with dementia residing in nursing homes was estimated to be about 40%.[173] The registration most commonly takes place in long-term care facilities, but the registry is used increasingly also in community and in short-term care facilities. The registry contains information about BPSD, the current medical therapy and a checklist for possible causes of BPSD.[174] The Neuropsychiatric Inventory-Nursing Home Version (NPI-NH)10 is used to assess BPSD, and it contains twelve categories of BPSD: delusions, hallucinations, agitation/aggression, depression/dysphoria, apathy, elation/euphoria, anxiety, disinhibition, irritability, aberrant motor behavior, sleep and night-time behavior changes and appetite and eating abnormalities.[27]

4.3 SWEDISH PRESCRIBED DRUG REGISTRY (SPDR)

SPDR was established in 2005 and covers the whole Swedish population. It includes information on drug dispensation from pharmacies.[175] It also includes basic sociodemographic information (age, sex), type of practice and profession of prescriber, as well as complete information on the dispensation (substance name, ATC code, date of prescribing and dispensing), dosage and expenditures.[175] The registry does not cover medicines that do not require a prescription or are used in hospital settings.[176]

4.4 SWEDISH CAUSE OF DEATH REGISTRY (CODR)

CODR has been accessible electronically since 1952 and is largely utilized in Sweden to estimate overall and specific mortality.[177] The whole Swedish population is covered in CODR. CODR data comes from medical death certificates, which must be completed within three weeks of a patient's death by a physician. The register includes information on the date, place

(e.g. hospital, nursing home), conditions that contributed to death and underlying causes of death according to the ICD coding.

4.5 SWEDISH NATIONAL PATIENT REGISTRY (NPR)

NPR has been collecting statistics on inpatient somatic and psychiatric care since 1964 reaching its complete coverage in 1987.[178] Four types of information are included in the registry: patient-related data (e.g. age, sex), caregiver data (hospital and department), administrative data (admission and discharge date), and medical data (diagnoses according to the ICD system).

4.6 DEFINITIONS AND VARIABLES TRANSFORMATIONS

4.6.1 BPSD

Assessments of BPSD were performed at the first entry to the BPSD registry using the NPI-NH,[27] based on information reported by a caregiver familiar with the individual's behavior. First, the frequency of symptoms is graded on a scale of 1 to 4 (1: occasionally, 2: less than once a week, 3: very frequently, 4: more than once a day). Second, the severity of the behavior is classified as: 1: mild, 2: moderate, or 3: severe. The NPI-NH assigns a value between 1 and 12 to each category by multiplying the frequency and severity scores. The total NPI score is computed by summing up all of the categories' scores with a maximum of 144 points. Scores of four or more in a given category are considered clinically significant.[179] BPSD were used as an outcome in studies 1 and 2.

4.6.2 Dementia

All dementia diagnoses registered by SveDem were included in Studies 1-2. In Studies 2-4, individuals with "other dementia" were omitted from the study. Early-onset and late-onset AD were grouped together as AD in all studies. Individuals diagnosed with DLB and PDD were grouped together as “Lewy body dementia” (LBD) in Studies 1,2, and 4. In addition, all studies included MMSE scores at the time of dementia diagnosis, which were obtained from SveDem and used as a covariate.

4.6.3 Medication

In all studies, the use of medication was binarily defined as users and non-users. We used the following sources to extract data regarding drug's prescription or dispensation: SveDem (Study 1 and 4), the BPSD registry (Study 1 and 2) and SPDR (Study 3).

In the SveDem registry, each patient's current medication prescription is recorded at the time of diagnosis with the possible answers 'yes'/'no'/'do not know'. The following medications are recorded in the registry: analgesics, antipsychotics, anxiolytics, hypnotics, antidepressants, acetylcholinesterase inhibitors (AChEI) and N-Methyl-D-aspartate (NMDA) receptor antagonist.

In the BPSD registry, information about medical treatment is collected at the time of BPSD assessment with the possible answers 'yes'/'no'/'do not know'. Specifically, the Anatomical Therapeutic Chemical (ATC) codes for the following medications were recorded: analgesics, antipsychotics (N05A), anxiolytics (N05B), hypnotics (N05C), antidepressants (N06AA), acetylcholinesterase inhibitors (AChEI) (N06DA) and N-Methyl-D-aspartate (NMDA) receptor antagonist (N06DX).

For Study 3, information about APD dispensation at dementia diagnosis was extracted from SPDR. We used the following Anatomical Therapeutic Chemical Classification System codes (see: http://www.whocc.no/atc_ddd_index) for antipsychotics classes to classify them into typical and atypical APD: typical: N05AA phenothiazines with aliphatic side-chain, N05AB phenothiazines with piperazine structure, N05AD butyrophenone derivatives, N05AF thioxanthene derivatives; atypical: N05AE indole derivatives, N05AH diazepines, oxazepines, thiazepines, and oxepines, and N05AX other antipsychotics. In this study, typical and atypical APD dispensation at the time of dementia diagnosis was used as an exposure.

4.6.4 Other covariates

Age, sex and living arrangements (living alone in ordinary housing, with somebody else in ordinary housing, or in a long-term care facility) were extracted from SveDem for all individuals. Age and sex were used as covariates in all studies, while living arrangements were considered only in Studies 3 and 4. The Charlson Comorbidity Index (CCI) was calculated by extracting ICD-10 codes from the NPR for chronic diseases other than dementia.[180] CCI contains 19 diseases including diabetes with diabetic complications, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, mild and severe liver disease, hemiplegia, renal disease, leukaemia, lymphoma, metastatic tumor, and acquired

immunodeficiency syndrome (AIDS), each of which was weighted according to their potential influence on mortality. The CCI score was used as a covariate in Study 1.

4.6.5 All-cause mortality

All-cause mortality was used as an outcome in Study 3. The outcomes were defined based on mortality as recorded in the CODR. The death of a person was counted if a valid record in the CODR existed (date of death dated after the study baseline).

4.6.6 Firearm status

SveDem contains the information about the firearm status of the individuals as well as whether the person was reported to the police as unsuitable to possess the firearm. The latter was used as an outcome in Study 4.

4.6.7 Unmet needs

To assess the relationships between unmet needs and different BPSDs, the checklist for possible causes of BPSD was performed at the first registration to BPSD registry (Panel 1). The checklist's items were chosen based on clinical experience. A caregiver assesses the unmet needs based on their observations of the individual. The elements in the checklist can be rated as "yes" or "no." Items marked with a "no" indicate that there are unmet needs. For example, the question for the item "Pain" is "does the individual appear to be free of suffering?" and the answer "no" indicates pain. The total unmet needs score was computed by adding the number of items on the checklist on which an individual answered "no," resulting in a score ranging from 0 to 14. Individual’s unmet needs as well as the total unmet needs score were used as an exposure in Study 2.

Panel 1. List of unmet needs

Sufficient Food
Sufficient Fluids
Normal Urine
Normal Faeces
Normal Sight
Normal Hearing
Free of pain
No social isolation
Normal sleeping
Normal temperature
Normal pulse
Normal breathing
Normal blood Pressure
Normal blood sugar

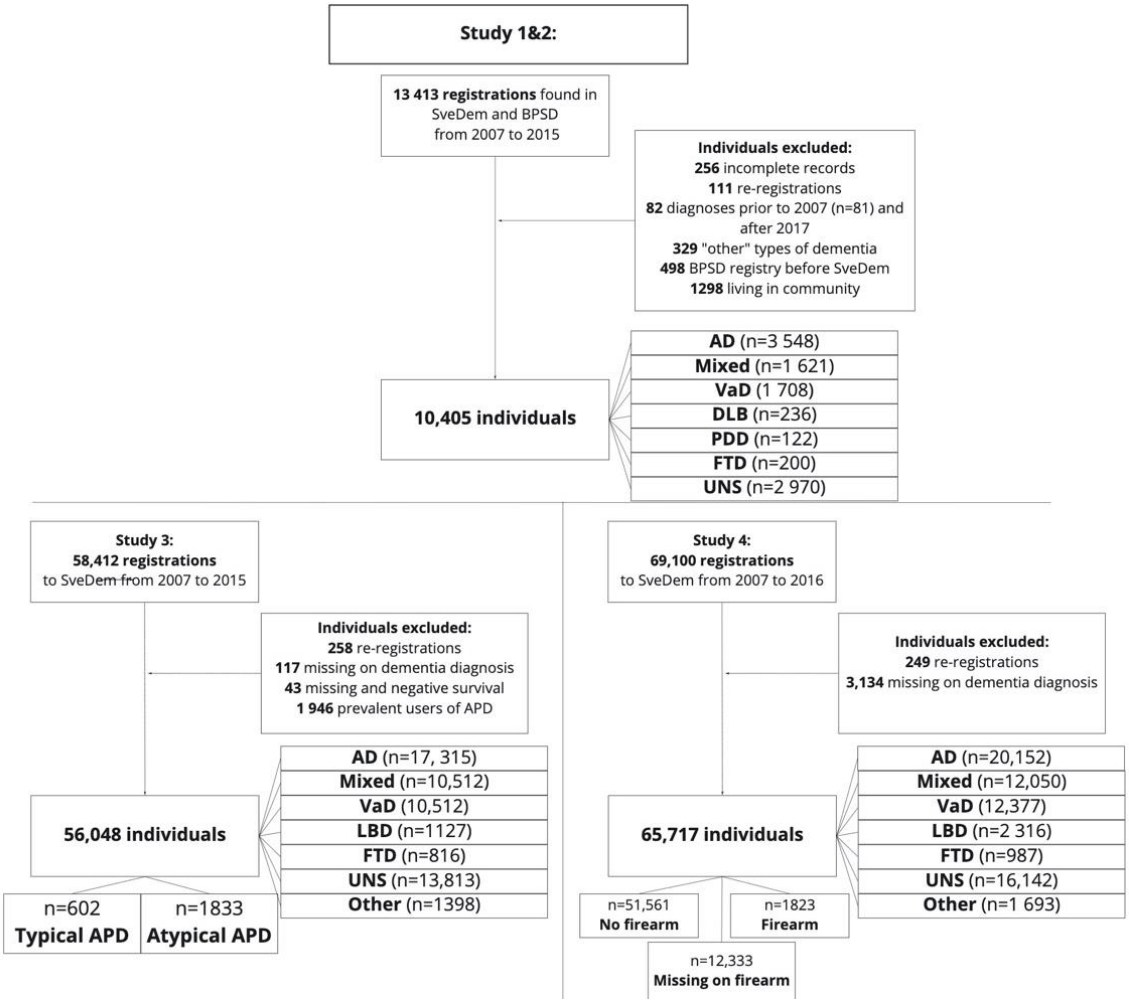
4.7 STUDY SAMPLES

For Studies 1-2, data from SveDem was merged with data from the BPSD registry (individuals registered between 2007 and 2015). After merging the data, 13,413 individuals registered in both registries were identified. The cohort included only individuals residing in long-term care facilities. After excluding individuals residing in a community and applying other exclusion criteria, we reached a sample size of 10,405 individuals (Figure 1).

In Study 3, we included 58,412 individuals with dementia that were registered in SveDem until December 31st, 2015. SveDem was merged with SPDR, CODR, and SNP and exclusion criteria were applied reaching a total of 56,048 individuals included in the final sample (Figure 1).

For Study 4, we used the information about individuals registered in SveDem between May 2007 to December 31st, 2016 (n = 69,100). After applying the exclusion criteria, we obtained the final study sample comprising of 65,717 individuals. For the main analyses, only individuals with firearms were selected (n = 1 823) (Figure 1).

Figure 1. The analytical samples extracted for the studies.



AD - Alzheimer Disease, Mixed - Mixed Dementia, VaD – Vascular dementia, DLB – Dementia with Lewy Bodies, PDD – Parkinson's disease dementia, FTD – Frontotemporal dementia.

4.8 STATISTICAL METHODS

All analyses were undertaken in R version 3.6.0 (Foundation for Statistical Computing, Vienna, Austria).[181] In all studies, continuous variables were summarized as mean and standard deviation (SD) or median and interquartile range, while categorical variables were summarized as the number of individuals and percentages. In univariate comparisons, the independent-samples t-test and one-way ANOVA were used to compare continuous variables, while Fisher-exact and the $\chi 2$ test were used to compare categorical variables. Specific methods used in individual studies are described below and in Table 1. For all studies a p-value <0.05 (corresponding to 95% CI) was considered statistically significant.

Study 1

Multivariate logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of having a clinically significant BPSD (NPI score > 3 in each category) compared to no symptom in each diagnosis compared to AD. The studies were then performed with each diagnosis as a control group. All models were adjusted for age, sex, MMSE and time between SveDem and BPSD registries.

Study 2

To find an association between the total unmet needs score and the total NPI score, we first built a linear regression model between the total unmet needs score as an independent variable and the total NPI score as an outcome in the whole cohort. This model was adjusted for the type of diagnosis, age, gender, MMSE score and time between registration to SveDem and the BPSD registry. Next, we stratified the cohort by the type of diagnosis, and performed linear regression analyses in each diagnostic group, adjusting for age, gender, MMSE score and time between time between entry to SveDem and BPSD registries. Finally, in each model, variable importance was estimated with a dominance analysis (DA).[182]

Secondary analyses

The relationship between specific unmet needs and BPSD was investigated in secondary analyses. We used multivariate logistic regression analysis to estimate Odds ratios (OR) and 95% Confidence Intervals (CIs) for the relationship between the individual unmet needs and

clinically significant BPSD (ref. no symptom). Variable selection was performed in 5 steps, as described below.

Step 1. To select unmet needs for multivariate logistic regression analysis, we first applied univariable logistic regression analysis with each independent variable (unmet need) and each BPSD separately. Variables with $p < 0.05$ were selected for the next step.

Step 2. We fitted multivariate logistic regression models containing all covariates identified for inclusion in Step 1. Each model was adjusted for age, gender, MMSE score, and time between registration to SveDem and BPSD registries.

Step 3 and 4. Variables with $p > 0.05$ in multivariate logistic regression analysis were removed from the models.

Step 5. All multivariate models were evaluated with Akaike information criterion (AIC).

Because of the low number of cases, we excluded the following unmet needs from the analyses: abnormal temperature, abnormal pulse, abnormal breathing. Additionally, to avoid conflicting exposer with the outcome, we excluded the following variables: not sufficient food and sleeping impairment in models for appetite and eating abnormalities and sleep and night-time behavior changes, respectively.

Study 3

The median survival time was calculated using the Kaplan-Meier method, and the median length of follow-up was calculated using the reverse Kaplan-Meier method.[183] The proportionate hazard assumption for the main predictors was verified by plotting the Schoenfeld residuals as a function of time and testing the hypothesis of a zero slope. Following that, separate Cox multivariate regression models were generated for the entire cohort and stratified by dementia type to evaluate the risk of mortality related with APD usage compared to nonuse. These models yielded crude and adjusted hazard ratio (HR) values, as well as associated 95% confidence intervals (CIs). Age at dementia diagnosis, MMSE, CCI, sex, and living arrangement (living alone in ordinary housing, with somebody else in ordinary housing, or in a long-term care facility) were all included into the final model. Finally, we repeated the analysis to compare users of typical and atypical APDs.

Due to violation of the assumption for proportional hazard in VaD, interactions with time were used to model the association in this diagnosis. To this end, we inspected residual plots and divided data into two epochs of the first 360 days and greater than that. Separate hazard

functions were fitted for each time-band. To this end, we inspected residual plots and divided data into two epochs of the first 360 days and greater than that. Separate hazard functions were fit for each time-band. Data were analysed with the Survival Package for R statistical software.[184]

Study 4

The odds ratios (ORs) and 95% confidence intervals (CIs) of the association between preselected factors and the outcome were estimated using multivariable logistic regression. Dementia subtype, gender, age, MMSE score (very severe: 0–10, moderate severe 11–18, moderate 19–23, mild 24–30), hypnotics, antipsychotics, anxiety suppressors, antidepressants, N-Methyl-D-aspartate receptor antagonist, acetylcholinesterase inhibitors, vascular medication, living arrangement (living alone in ordinary housing, with somebody else in ordinary housing, or in a long-term care facility), and diagnosing unit (primary care, memory clinic) were assessed as potential predictors of the outcome, which was being reported to the police as unsuitable to own firearm.

Discrimination ability of the model was evaluated by bootstrapped area under the receiver operating characteristic curve (AUC).[185] Finally, variable importance was estimated with fully standardized coefficients (SC) and DA.

4.9 ETHICAL CONSIDERATIONS

In epidemiology and public health practice, ethical considerations frequently revolve around the responsibility of health professionals' responsibility to obtain and utilize scientific information in order to preserve and restore public health while protecting individual rights.[187] Potential social advantages must frequently be weighed against risks and potential costs to people and groups, such as stigmatization and violations of privacy of privacy. Although the hazards offered by epidemiologic research are often small in comparison to those posed by clinical trials and other experimental investigations, participants in epidemiologic studies may face a loss of privacy or stigmatization. The Council of International Organizations of Medical Sciences issued international criteria for ethical evaluation of epidemiology studies.[188] The institutional review board system, informed consent, avoiding and disclosing conflicts of interest, minimizing risks and providing benefits, and the obligations to communities are the issues highlighted in ethics guidelines.

The goal of research ethics committees is to guarantee that studies involving human research subjects are planned in accordance with applicable ethical standards and that the participants' rights and welfare are respected. Human-subjects assessment by such committees guarantees that research has a good balance of potential benefits and risks, that participants are selected equitably, and that informed consent processes are acceptable. The regional ethical review board in Stockholm, Sweden, authorized all operations involving human subjects/patients, with the following ethical numbers: 2015/2291-31/5 (Studies 1 and 2) and 2015/2232-31 (Studies 3 and 4). In addition, part of my PhD research was dedicated to recruiting participants for the multicenter European project Remote Assessment of Disease and Relapse-Alzheimer's disease (RADAR-AD), which investigated the potential of mobile technology in enhancing the quality of care for people with Alzheimer's disease.[189] We received a separate ethical approval for this study with the number 2020-03497. According to the protocols in SveDem and BPSD registry, individuals with dementia and their relatives are provided oral and written information about the goals of the studies and can refuse to participate. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. To avoid the conflicts of interest, all researchers involved in the study disclosed their financial interests and funding sources before publishing their findings.

In epidemiologic studies of vulnerable groups, minimizing risks and possible harms while optimizing potential benefits is crucial. The rigorous protection of the anonymity of

participants' health information is an important strategy for public health researchers to prevent possible harms and hazards to them in epidemiologic studies. To ensure the confidentiality of the participants' health information, rigorous measures were implemented. Personal identifiers were removed from data. After the ethical application had been accepted by the ethical committee, the data were anonymized and it is not possible to reverse the anonymization. Additionally, data were solely evaluated at the group level, with no subject-level analysis. The potential benefits of our studies are mostly social in nature. Although participants may not gain immediate benefits as a result of their involvement in the study, our findings aid in the gathering of new knowledge regarding the parameters linked to improved quality of life of individuals with dementia. The underlying objective of our study is to get a comprehensive understanding of the factors associated to BPSD. Registry-based data provide substantial benefit by enabling merging several different registries together as well as large number of registered individuals.

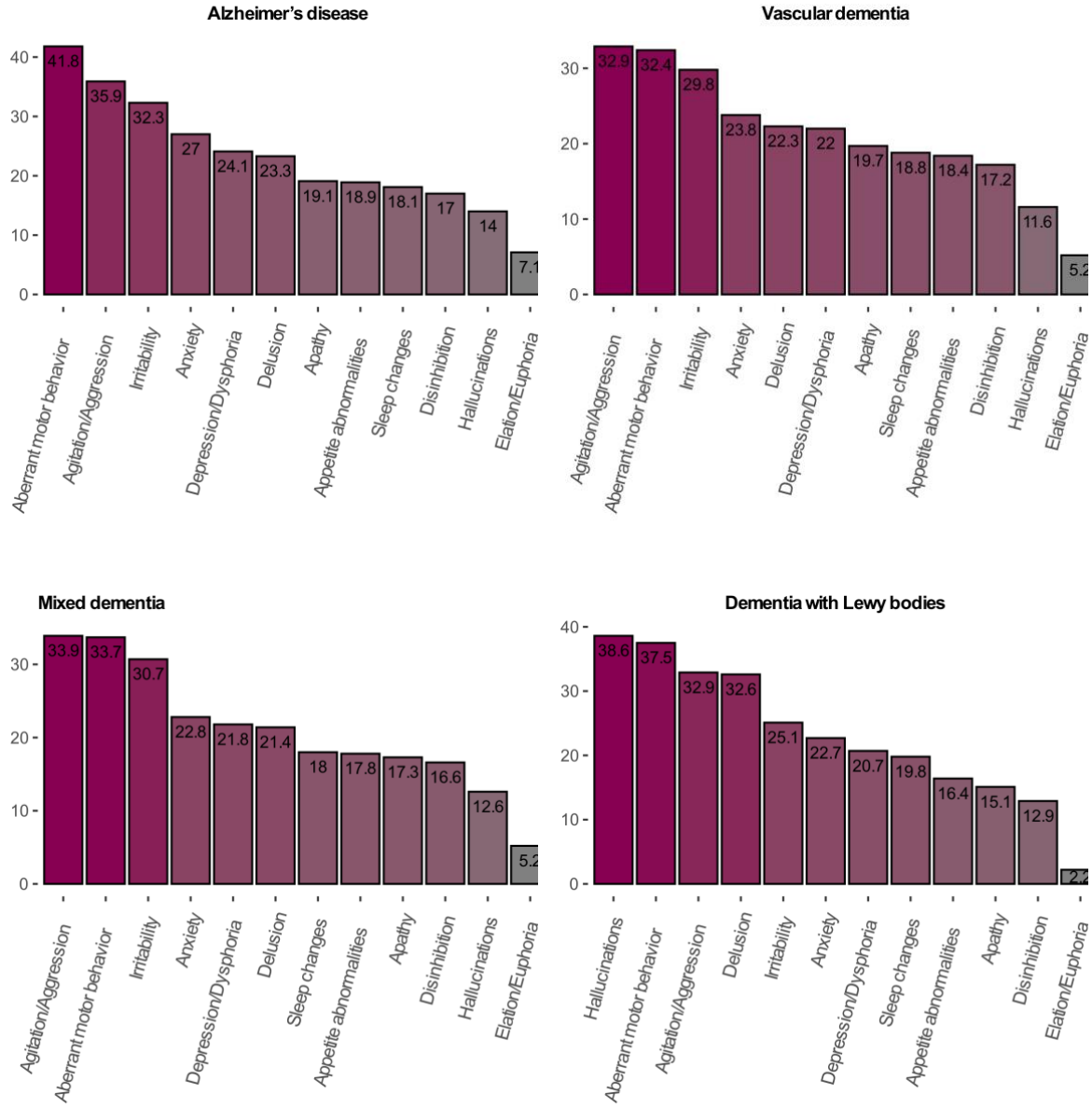
We took an active role in popularizing the finding of our research. For example, we presented our research in ForskarFredag (Researchers' Friday). The event is organized by the non-profit organization Vetenskap & Allmänhet in Sweden (Public & Science). Additionally, results of the Study 3, were published in Swedish medical journal Läkartidningen (Läkartidningen 19–20/2019; "Antipsykotika förknippade med ökad mortalitet vid demens"). Results of the Study 4 were disseminated as a press release. I was also responsible for organizing and moderating webinar "Technology in Dementia: promises and barriers identified by the RADAR-AD project", where we discussed details concerning RADAR-AD project (project not included in the Thesis).

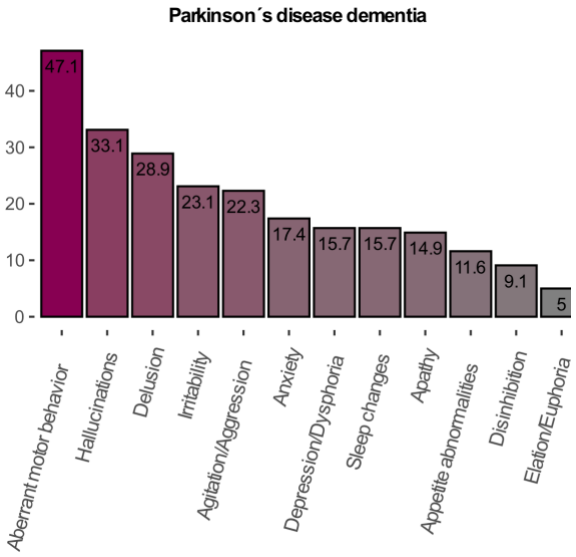
5 RESULTS

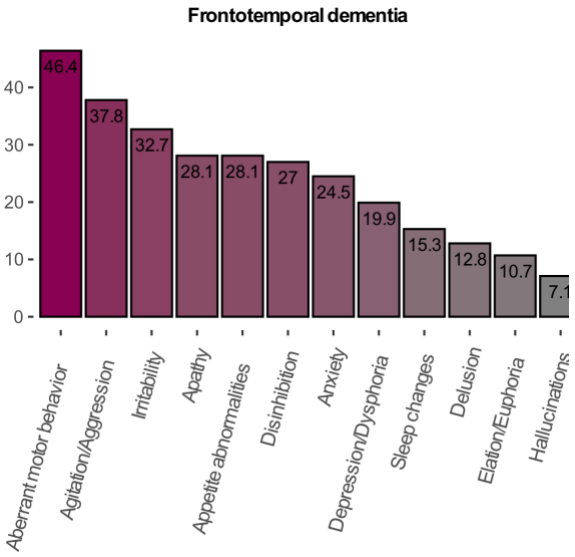
5.1 BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS ARE FREQUENT IN ALL TYPES OF DEMENTIA (STUDY 1)

In Study 1, we found that 75% of all individuals with dementia had at least one clinically significant BPSD, with the most common being aberrant motor behavior, agitation/aggression and irritability. The frequencies of BPSD in each diagnosis are presented in Figure 2. The multivariate logistic regression analyses showed that, compared to AD, individuals with VaD had higher risk of apathy but lower risk of agitation/aggression, anxiety, aberrant motor behavior; individuals with Mixed dementia had lower risk of clinically significant anxiety and aberrant motor behavior; individuals with DLB had higher risk of delusions and hallucinations and lower risk of elation/euphoria and irritability; individuals with PDD had higher risk of hallucinations but lower risk of agitation/aggression and disinhibition, individuals with FTD had higher risk of apathy, disinhibition, appetite and eating abnormalities as well as lower risk delusion, hallucinations, depression/dysphoria; individuals with UNS had lower risk of delusion, agitation/aggression, depression/dysphoria, anxiety, irritability, aberrant motor behavior, sleep and night-time behavior (Table 1). Short summary of comparisons between diagnoses is presented in Table 2.

Figure 2. Frequency of clinically significant BPSD across different dementia diagnosis




Parkinson´s disease dementia
47.1
33.1
28.9
23.1
22.3
17.4
15.7
15.7
14.9
11.6
9.1
5
Aberrant motor behavior
Hallucinations
Delusion
Irritability
Agitation/Aggression
Anxiety
Depression/Dysphoria
Sleep changes
Apathy
Appetite abnormalities
Disinhibition
Elation/Euphoria


Frontotemporal dementia
46.4
37.8
32.7
28.1
28.1
27
24.5
19.9
15.3
12.8
10.7
Aberrant motor behavior
Agitation/Aggression
Irritability
Apathy
Appetite abnormalities
Disinhibition
Anxiety
Depression/Dysphoria
Sleep changes
Delusion
Elation/Euphoria
Hallucinations

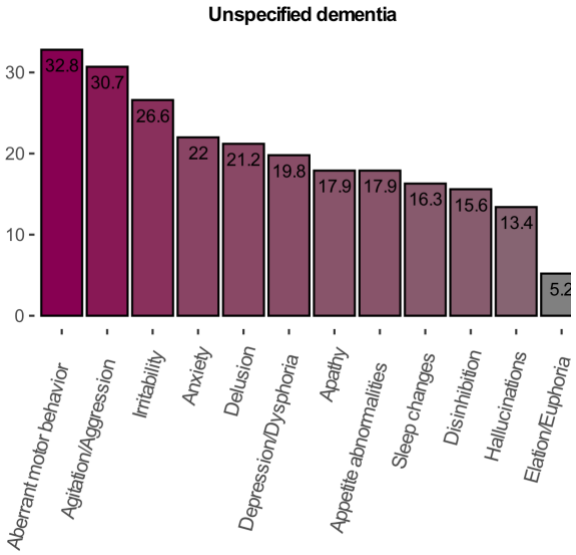

Unspecified dementia
32.8
30.7
26.6
22
21.2
19.8
17.9
17.9
16.3
15.6
13.4
Aberrant motor behavior
Agitation/Aggression
Irritability
Anxiety
Delusion
Depression/Dysphoria
Apathy
Appetite abnormalities
Sleep changes
Disinhibition
Hallucinations
Elation/Euphoria

Table 1. Odds ratios (OR) and 95% confidence intervals (CI) of the association between dementia type and BPSD with the reference to AD in individuals residing in long-term care facility.

	VaD		Mixed		DLB		PDD		FTD		UNS	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Delusions	0.95 (0.82-1.11)	0.542	0.91 (0.78-1.06)	0.234	**1.71 (1.25-2.33)**	**0.001**	1.35 (0.85-2.1)	0.185	**0.44 (0.27-0.68)**	**<0.001**	**0.87 (0.77-1)**	**0.044**
Hallucinations	0.83 (0.69-1.01)	0.066	0.94 (0.78-1.13)	0.54	**5.94 (4.31-8.2)**	**<0.001**	**4.47 (2.86-6.95)**	**<0.001**	**0.5 (0.27-0.85)**	**0.016**	1.01 (0.86-1.18)	0.93
Agitation/Aggression	**0.85 (0.73-0.98)**	**0.029**	1.01 (0.87-1.17)	0.905	0.84 (0.61-1.16)	0.291	**0.46 (0.28-0.75)**	**0.002**	0.97 (0.67-1.41)	0.871	**0.85 (0.75-0.96)**	**0.011**
Depression/Dysphoria	0.94 (0.8-1.1)	0.465	0.93 (0.79-1.09)	0.361	1.01 (0.69-1.45)	0.964	0.69 (0.39-1.16)	0.181	**0.57 (0.38-0.85)**	**0.007**	**0.83 (0.72-0.95)**	**0.007**
Elation/Euphoria	0.9 (0.69-1.18)	0.463	0.89 (0.68-1.16)	0.395	**0.32 (0.11-0.71)**	**0.014**	0.79 (0.3-1.69)	0.58	1.25 (0.72-2.05)	0.405	0.89 (0.7-1.11)	0.307
Anxiety	**0.85 (0.73-0.98)**	**0.031**	**0.82 (0.71-0.96)**	**0.012**	0.83 (0.58-1.16)	0.282	0.64 (0.37-1.06)	0.097	0.73 (0.49-1.07)	0.11	**0.75 (0.66-0.85)**	**<0.001**
Apathy	**1.21 (1.03-1.42)**	**0.023**	1.04 (0.88-1.22)	0.684	0.87 (0.58-1.26)	0.471	0.89 (0.5-1.49)	0.678	**1.54 (1.06-2.22)**	**0.022**	1.09 (0.94-1.25)	0.256
Disinhibition	1.03 (0.87-1.22)	0.714	1.02 (0.86-1.21)	0.816	0.71 (0.46-1.05)	0.097	**0.4 (0.19-0.74)**	**0.007**	**1.52 (1.03-2.2)**	**0.03**	0.97 (0.83-1.12)	0.683
Irritability	0.94 (0.81-1.08)	0.381	1.08 (0.93-1.24)	0.322	**0.67 (0.47-0.93)**	**0.018**	0.65 (0.4-1.04)	0.081	**0.69 (0.48-0.98)**	**0.042**	**0.83 (0.73-0.95)**	**0.005**
Aberrant motor behavior	**0.66 (0.58-0.76)**	**<0.001**	**0.75 (0.66-0.86)**	**<0.001**	0.75 (0.55-1)	0.053	1.12 (0.74-1.68)	0.594	0.83 (0.59-1.15)	0.257	**0.73 (0.65-0.82)**	**<0.001**
Sleep and night-time behavior changes	0.92 (0.78-1.08)	0.317	0.91 (0.77-1.07)	0.267	0.98 (0.67-1.4)	0.917	0.66 (0.37-1.13)	0.148	0.82 (0.51-1.26)	0.381	**0.82 (0.71-0.95)**	**0.008**
Appetite and eating abnormalities	1.08 (0.92-1.27)	0.33	1.02 (0.87-1.2)	0.809	0.92 (0.62-1.32)	0.649	0.63 (0.34-1.07)	0.109	**1.84 (1.27-2.63)**	**0.001**	1 (0.87-1.15)	0.998

AD - Alzheimer Disease, Mixed - Mixed Dementia, VaD – Vascular dementia, DLB – Dementia with Lewy Bodies, PDD – Parkinson's disease dementia, FTD – Frontotemporal dementia, UNS – Unspecified dementia. Model adjusted for age, sex, MMSE and time between registration to SveDem and BPSD registry.

Table 2. Summary of the differences in BPSD in individuals residing in long-term facility based on logistic regression analyses.

	AD	VaD	Mixed	DLB	PDD	FTD	UNS
Delusions	AD< FTD, UNS; AD>DLB	VaD>DLB; VaD<FTD	Mixed>DLB; Mixed < FTD	DLB<AD, Mixed, VaD, FTD, UNS	PDD<FTD	FTD>AD, Mixed, VaD, DLB, PDD, UNS	UNS>AD, DLB; UNS<FTD
Hallucinations	AD< FTD; AD>DLB, PDD	VaD>DLB, PDD;	Mixed> DLB, PDD; Mixed < FTD	DLB<AD, Mix, VaD, FTD, UNS	PDD<AD, Mixed, VaD, FTD, UNS;	FTD>AD, Mixed, DLB, PDD, UNS	UNS>DLB,PDD; UNS<FTD
Agitation/Aggression	AD<VaD, PDD, UNS	VaD<PDD; VaD>AD, Mixed	Mixed<VaD, PDD, UNS	DLB<PDD	PDD>AD, Mixed, VaD, DLB, FTD, UNS	FTD<PDD	UNS>AD, Mixed; UNS<PDD
Depression/Dysphoria	AD<FTD, UNS	VaD<FTD	Mixed<FTD	DLB<FTD		FTD>AD, Mixed, VaD, DLB	UNS>AD
Elation/Euphoria	AD<DLB	VaD<DLB	Mixed<DLB	DLB>AD, Mixed, VaD, FTD, UNS		FTD<DLB	UNS<DLB
Anxiety	AD<Mixed,VAD UNS	VaD<AD	AD>Mixed				UNS>AD
Apathy	AD>VaD, FTD		Mixed>FTD	DLB>FTD		FTD<AD, Mixed, DLB,	
Disinhibition	AD<PDD; AD>FTD	VaD<PDD	Mixed<PDD Mixed>FTD	DLB>FTD	PDD>Mixed, VaD, FTD, UNS	FTD<AD, Mixed, DLB, PDD, UNS	UNS<PDD; UNS>FTD
Irritability	AD<DLB, FTD, UNS		Mixed<DLB, PDD, FTD, UNS	DLB>AD, Mixed	PDD>Mixed	FTD>AD, Mixed	UNS>AD, Mixed
Aberrant motor behavior	AD<Mixed, VaD, UNS	VaD>AD, PDD	Mixed>AD		PDD<VaD PDD > UNS		UNS>AD UNS<PDD
Sleep and night-time behavior changes	AD<UNS						UNS>AD
Appetite and eating abnormalities	AD>FTD	VaD>FTD	Mixed>FTD	DLB>FTD	PDD>FTD	FTD<AD, Mixed, VaD, DLB, PDD, UNS	UNS>FTD

Diagnosis > ref - Diagnosis Less than ref: Diagnosis < ref - Diagnosis More than ref; AD - Alzheimer Disease; Mixed - Mixed Dementia; VaD – Vascular dementia; DLB – Dementia with Lewy Bodies; PDD- Parkinson's disease dementia; FTD – Frontotemporal dementia; UNS – Unspecified dementia.

5.2 UNMET NEEDS ARE RELATED TO INCREASED RISK OF BPSD (STUDY 2)

The results of Study 2 showed that pain was the most common unmet need (29.1%) in individuals with dementia. This was followed by sleeping disturbances (15.3%), abnormal sight (15.1%) and abnormal hearing (15.0%) (Table 3). Linear regression models revealed an association between the unmet needs score and total NPI scores (beta=5.32, t=34.86, $p<0.001$) (Table 5). The results were similar when analyses were performed in each diagnosis separately. DA showed that the total unmet needs score had a general dominance over other variables in the model. The average contribution of each predictor to an overall model fit is presented in Table 4. Additionally, in the secondary analyses, we found that unmet needs manifest in a variety of behaviors. Pain, sleeping disturbances and social isolation were commonly associated with several symptoms in all types of dementia.

Table 3. Frequency of unmet needs across dementia subtypes

	Total	AD	Mixed	VaD	LBD	FTD	UNS	P.value
Insufficient Food	1124 (11)	389 (11,2)	183 (11,5)	171 (10,2)	39 (11,1)	18 (9,1)	324 (11,1)	0.787
Insufficient Fluids	790 (7.8)	281 (8.1)	132 (8.3)	116 (6.9)	34 (9.7)	10 (5.1)	217 (7.4)	0.211
Abnormal Urine	494 (4.9)	142 (4.1)	77 (4.9)	93 (5.6)	22 (6.3)	5 (2.5)	155 (5.3)	0.047
Abnormal Faeces	894 (8.8)	284 (8.2)	124 (7.8)	145 (8.7)	45 (12.9)	21 (10.7)	275 (9.4)	0.211
Abnormal Sight	1534 (15.1)	439 (12.7)	250 (15.8)	309 (18.5)	55 (15.7)	15 (7.6)	466 (16)	<0.001
Abnormal Hearing	1532 (15)	429 (12.4)	270 (17)	291 (17.4)	28 (8)	15 (7.6)	499 (17.1)	<0.001
Pain	2944 (29.1)	962 (28)	463 (29.4)	496 (29.8)	94 (27)	53 (26.9)	876 (30.2)	0.345
Social isolation	779 (7.7)	244 (7.1)	133 (8.4)	144 (8.6)	29 (8.3)	17 (8.7)	212 (7.3)	0.279
Sleeping problems	1556 (15.3)	542 (15.7)	264 (16.7)	277 (16.6)	52 (14.9)	24 (12.2)	397 (13.6)	0.029
Abnormal temperature	29 (0.3)	5 (0.1)	9 (0.6)	5 (0.3)	3 (0.9)	1 (0.5)	6 (0.2)	0.026
Abnormal pulse	186 (1.8)	53 (1.5)	36 (2.3)	40 (2.4)	5 (1.4)	2 (1)	50 (1.7)	0.208
Abnormal breathing	872 (8.7)	250 (7.3)	149 (9.5)	148 (9)	56 (16.1)	12 (6.1)	257 (8.9)	0.007
Blood Pressure	450 (4.5)	125 (3.7)	71 (4.5)	130 (7.9)	12 (3.5)	8 (4.1)	104 (3.6)	<0.001
Blood sugar	1124 (11)	389 (11.2)	183 (11.5)	171 (10.2)	39 (11.1)	18 (9.1)	324 (11.1)	<0.001

The data are presented as n (%). AD - Alzheimer Disease, Mixed - Mixed Dementia, VaD – Vascular dementia, LBD - Lewy body dementia, FTD – Frontotemporal dementia, UNS – Unspecified dementia. To assess differences between group we used Pearson Chi-Square test or Fisher's exact test.

Table 4. Dominance analysis and Linear Regression model for the association between variables used in the model and Neuropsychiatric Inventory (NPI) score.

	Linear regression model				Dominance analysis
	Coefficients	**Standard Error**	**t Stat**	**p**	**Weighting* (rank)**
Total unmet needs	4.84	0.15	33.36	<0.001	92.8 (1)
Diagnosis, ref:AD					3 (5)
Mixed	-1.55	0.57	-2.71	0.007	
VaD	-1.9	0.57	-3.33	0.001	
LBD	-0.86	1.07	-0.80	0.424	
FTD	0.13	1.42	0.09	0.929	
UNS	-2.06	0.51	-4.06	<0.001	
Male (ref: Female)	0.69	0.41	1.70	0.09	1 (6)
Age	-0.41	0.03	-15.64	<0.001	16 (2)
MMSE	-0.31	0.04	-8.05	<0.001	4.8 (3)
Time between registations, days	0 (0-0)	0.00	6.92	<0.001	2.4 (4)

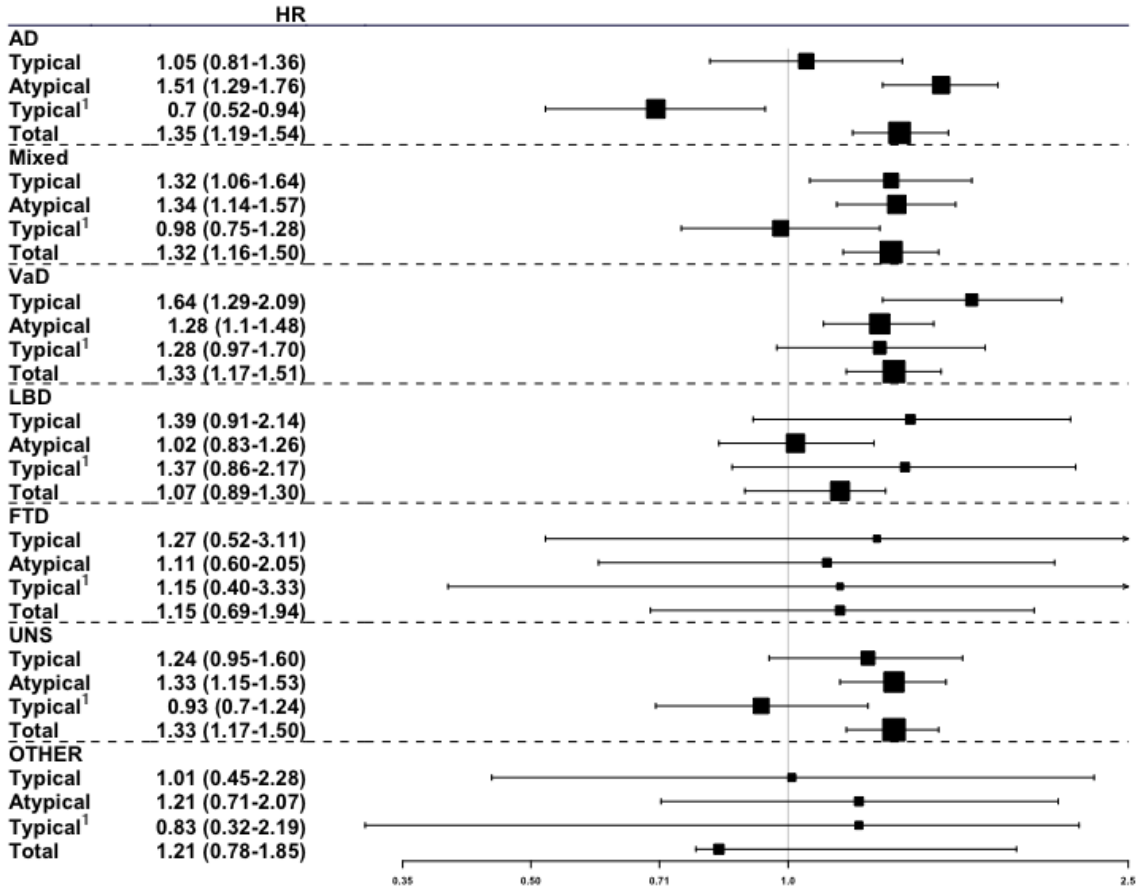
NPI – Neuropsychiatric Inventory, AD - Alzheimer Disease, Mixed - Mixed Dementia, VaD – Vascular dementia, LBD –Lewy Body Dementia, FTD – Frontotemporal dementia, UNS – Unspecified dementia, MMSE - Mini-Mental State Exam at the time of diagnosis, Time between registrations – days between entry to SveDem and BPSD registry, *multiplied by 1000.

5.3 APDS ARE ASSOCIATED WITH INCREASED MORTALITY RISK IN INDIVIDUALS WITH DEMENTIA (STUDY 3)

In the whole sample, 4% (n = 2526) of the individuals had an APD prescription: 602 had only typical APDs,1833 had only atypical APDs and ninety-one individuals had both typical and atypical APDs prescribed. There were differences in APD use between the different dementia diagnoses. Among individuals receiving APDs, typical APD use was lowest in individuals with LBD (13%), followed by other (23%), VAD (24%), FTD (24%), UNS dementia (25%), AD (26%), and mixed dementia (32%). Atypical use was lowest in Mixed (68%), followed by AD (74%), UNS dementia (75%), VAD (76%), FTD (76%), other (77%), and LBD (87%).

Use of typical and atypical APDs was associated with increased mortality risk compared with no APD use in the entire cohort [HR (95% CI)]. Typical APDs increased the risk of death by 1.4 (1.2-1.5) and atypical APDs by 1.4 (1.3-1.5) (adjusted for sex, age, MMSE, CCI, and form of residency)]. Statistically significant associations between APD use and increased risk of mortality compared with non-APD use were also found when the cohort was stratified by the subtypes of dementia (Figure 3).

Figure 3. Cox multivariate analyses assessing all-cause mortality risk associated with APD for different dementia diagnoses.



Total- entire cohort; AD – Alzheimer Disease, Mixed – Mixed Dementia, LBD – Lewy body dementia, FTD – Frontotemporal dementia, UNS – Unspecified dementia, APD - Antipsychotic; Adjusted for Age, Gender, MMSE, CCI, Living. VaD: Assuming proportional hazard; Typical and Atypical compared to no APD; Typical[1] compared to atypical APD, Total (typical+atypical) compared to no APD.

5.4 ENVIRONMENTAL, PATIENT-RELATED AND SYSTEM FACTORS ARE ASSOCIATED WITH INCREASED RISK OF BEING REPORTED TO THE AUTHORITY AS UNSUITABLE TO OWN A FIREARM (STUDY 4)

We identified 1,823 (3.4%) individuals with dementia who owned a firearm. Out of those, 346 individuals were reported to the police by the physicians as unsuitable to own a firearm. Additionally, 73 individuals were reported despite the lack of information on their firearms status. Compared to individuals with dementia who did not own firearm, firearm owners were younger (age < 79 years: 53.4% versus 38.8%), predominantly male (90.4% versus 38.7%), living alone (71.5% versus 46.7%), and without assistance of homecare (17.8% versus 33.4%). The distribution of other characteristics was similar between the two groups. Almost 19% of persons had missing information on the firearm status.

According to dominance analysis, the most important characteristics used by physicians were: 1) living arrangement, 2) dementia subtype, 3)APD prescription, 4) diagnosing unit, 5) sex, and 6)MMSE score. Somewhat similar, the most important factors in terms of the SC were: diagnosing unit (being diagnosed in primary care versus memory clinic, SC = -0.27), followed by mild dementia (MMSE 24–30 versus 0–10, SC = -0,25), living arrangements (living with someone else in the household versus living alone, SC = 0.23), moderate dementia (MMSE 19–23 versus 0–10, SC = -0.21), antipsychotics prescription (SC = 0.18), dementia subtype (FTD versus AD, SC = 0.18), female gender (SC = 0.18), and hypnotics (SC = 0.17). Of these, following predictors were associated with higher odds of being reported to the police as unsuitable to possess firearm [OR (95% CI)]: living with someone else in household [1.67 (1.17–2.38)], hypnotics [1.77 (1.21–2.59)] or antipsychotics [2.42 (1.35–4.35)] prescription, being diagnosed with FTD [3.1 (1.56–6.18)], and being a female [1.79 (1.2–2.67)]. On the other hand, being diagnosed in a primary care clinic [0.59 (0.44–0.78)] and with mild [0.60 (0.32–1.13)] or moderate [0.65 0.35–1.22)] dementia were associated with lower odds of being reported. The pooled bootstrapped AUC of the model was 0.66. The full model is presented in the Table 5.

Table 5. Odds ratios (OR) and 95% confidence intervals (CI) and the relative importance indicators (standardized coefficients (SC) and dominance rank (DR) based on the standardized general dominance statistic (SGDS)) of the association between predictors and being reported to the police as unsuitable to own a firearm.

	OR (95%CI)	SC	SGDS	DR
Diagnosis				
Alzheimer's Disease	Ref	Ref		
Frontotemporal dementia	3.1 (1.56-6.18)	0.180		
Lewy body dementia	0.89 (0.53-1.5)	-0.030		
Mixed dementia	1.45 (1.06-2.16)	0.149	0.011	2
Vascular dementia	1.38 (0.88-2.16)	0.131		
Other	1.59 (0.75-3.36)	0.075		
Unspecified	1.21 (0.83-1.78)	0.080		
Age				
<74	Ref	Ref		
74-78	1.22 (0.74-2)	0.053	0.0026	9
79-84	1.22 (0.75-2)	0.051		
>84	0.89 (0.51-1.55)	-0.074		
Gender				
Female vs Male	1.79 (1.2-2.67)	0.177	0.0084	5
Mini-Mental State Examination				
Very severe (0-10)	Ref	Ref		
Moderate severe (11-18)	0.97 (0.5-1.9)	-0.012	0.0072	6
Moderate (19-23)	0.65 (0.35-1.22)	-0.209		
Mild (24-30)	0.6 (0.32-1.13)	-0.245		
Living arrangements				
Living alone	Ref	Ref		
Nursing Home	2.14 (1.25-3.64)	0.152	0.0166	1
Living with another person	1.67 (1.17-2.38)	0.232		
Diagnosting unit				
Primary care vs. Memory Clinic	0.59 (0.44-0.78)	-0.266	0.0094	4
Daycare				
Yes vs. no	0.87 (0.4-1.89)	-0.030	0	14
Homecare				
Yes vs. no	1.18 (0.86-1.63)	0.063	0.0028	8
N-Methyl-D-aspartate receptor antagonists				
Yes vs. no	0.94 (0.59-1.5)	-0.009	0	14
Acetylcholinesterase inhibitors				
Yes vs. no	0.91 (0.66-1.27)	-0.050	0.002	10
Vascular drugs				
Yes vs. no	0.84 (0.65-1.08)	-0.084	0.0014	12
Antidepressants				
Yes vs. no	0.74 (0.52-1.06)	-0.135	0.0018	11
Antipsychotics				
Yes vs. no	2.42 (1.35-4.35)	0.184	0.0098	3
Hypnotics				
Yes vs. no	1.77 (1.21-2.59)	0.171	0.0072	7
Anxiety suppressors				

Yes vs. no	0.88 (0.56-1.37)	-0.033	0	14

6 DISCUSSION

6.1 DIFFERENCES AND SIMILARITIES IN BPSD ACROSS SUBTYPES OF DEMENTIA (STUDY 1)

We found that BPSD is prevalent across all dementia types, with approximately 75% of all individuals having at least one clinically significant BPSD. The most prevalent symptoms were abnormal motor behavior, agitation, and irritability.

AD, VaD, and Mixed

Aberrant motor behavior, agitation/aggression, and irritability were the most prevalent clinically significant symptoms in AD, Mixed, and VaD. We found that individuals with AD had a greater risk of anxiety, abnormal motor behavior, and agitation when compared to individuals with Mixed and VaD. On the other hand, individuals with VaD exhibited a higher risk of apathy than those with AD. The sole difference between individuals with Mixed and VaD was a higher risk of agitation/aggression in individuals in Mixed.

DLB and PDD

The most common symptoms in DLB were hallucinations, aberrant motor behavior and agitation/aggression and in PDD aberrant motor behavior, hallucinations and delusions. However, in adjusted analyses apart from a decreased likelihood of agitation/aggression in individuals with PDD compared to individuals with DLB, we found no major differences between the two diagnoses. Our study demonstrated a greater risk of hallucinations and delusions in DLB compared to other diagnoses. Individuals with DLB, on the other hand, showed a lower risk of elation/euphoria than those with any other kind of dementia, except for PDD. Anxiety and other hyperactivity spectrum symptoms (agitation/aggression, disinhibition, and irritability) were less common in those with PDD than in the remaining diagnoses.

FTD

The most common symptoms in FTD were aberrant motor behavior, agitation/aggression and irritability. Moreover, the highest total NPI score was found in this group of individuals. Additionally, in adjusted models, we discovered a higher risk of apathy (except for VaD, PDD, and UNS), disinhibition (except for VaD), appetite and eating abnormalities in FTD compared to the other dementia diagnoses, as well as a reduced risk of delusions, hallucinations (except

for VaD), and depression (except for PDD and UNS). In comparison to DLB, FTD had a greater probability of elation/euphoria.

UNS

In UNS, abnormal motor behavior, agitation/aggression, and irritability were the most prevalent symptoms. Additionally, this group had the lowest total NPI score. This was consistent with our findings of a decreased likelihood of numerous symptoms in UNS compared to other kinds of dementia.

General comment

In our cohort, the most prevalent symptoms were abnormal motor behavior, agitation, and irritability, which were found to be common in all dementias. Previous research that included individuals in long-term care facilities has similarly found high levels of hyperactive symptoms in this study settings.[190] However, to our knowledge, this is the first study to indicate that these symptoms occur often independent of dementia type. Certain characteristics of the long-term care facilities appear to enhance the incidence of BPSD.[89] The perception of the environment and coping capacities are affected by dementia-related processes.[33,34] Hyperactivity symptoms in individuals with dementia may be therefore the consequence of greater vulnerability to stresses and a higher susceptibility to over- or under-stimulation, which can lead to dysfunctional behaviors like agitation or irritability. Additionally, boredom-relieving behaviors like as pacing or wandering may be used to compensate for a lack of stimulation, which is prevalent in long-term care facilities.[92] The finding of BPSD consistency across diagnoses has implications for developing cost-effective therapies. Regardless of the underlying condition, our findings imply that if resources are limited, attempts to minimize agitation/aggression, aberrant motor behavior, and irritability should be prioritized.

6.2 THE ASSOCIATION OF UNMET NEEDS AND BPSD (STUDY 2)

Pain, sleeping problems, impaired hearing and vision were the most prevalent unmet demands. Furthermore, we found that an increase in the number of unmet requirements was linked to an increase in the overall NPI score, regardless of the type of dementia. Furthermore, the dominance analyses revealed that unmet needs contribute more to BPSD than the type of dementia, age or gender. In secondary analyses we observed that unmet needs present

themselves in a range of behaviors. Pain, sleep difficulties, and social isolation were all linked to a variety of symptoms in individuals with dementia.

General comment

This and several earlier studies indicate a link between unmet needs and BPSD.[29,30,92,191–193] However, the exact mechanisms behind this association are unknown. Caring for individuals with dementia is challenging due to their increasing inability to communicate their needs, especially as they move through the disease. [29,30] Therefore, BPSD might be triggered by an inability to convey ones' need or discomfort. Individuals who are understimulated, have pain or other sources of discomfort, but are unable to articulate their feelings, may become agitated or display other BPSD symptoms.[30,92,194–199] Furthermore, unmet needs may trigger a cascade of events in which one unmet need leads to another, resulting in BPSD.[31] Ignoring the basic physiological needs may also lead to dehydration, malnutrition or chronic constipation. Constipation in turn has been linked to agitation and anxiety in the past.[200,201] BPSD may also emerge as a compensation mechanism. For example, internal stimuli may be triggered to compensate for a lack of stimulation caused by limited social interaction or sensory impairment.[193] Additionally, there is a possibility that unmet needs and BPSD share a neuropathology. For example, neurodegeneration can result in unmet needs such as sleeping difficulties or sensory impairment.[202–204]

Clinical guidelines in Sweden recommend non-pharmacological interventions for BPSD before implementing drug therapies. Our findings highlight the need of identifying underlying unmet needs in persons with dementia, such as pain, social isolation, sleep, and vision impairment, as a cause of behavioral difficulties before administering psychotropic medication. Unmet needs constitute potentially modifiable factors contributing to BPSD. The evidence emphasizes the potential utility of effective pain therapy, sensory impairment treatment, and non-drug therapies in lowering BPSD as well as the use of psychotropic medicines.[205–209] Despite the paucity of high-quality evidence for sleep disorders therapies, there are some possibilities for non-pharmacological and pharmacological therapy of sleep problems in dementia.[160,210,211]

6.3 TREATMENT WITH ANTIPSYCHOTICS AND MORTALITY (STUDY 3)

APDs were used by 4% of individuals with newly diagnosed dementia and their usage was associated with an increased risk of mortality. In individuals with AD, typical APDs were associated with similar mortality risk as lack of APDs and only atypical APDs were related to a higher risk of mortality. To our knowledge, this has not been previously described. Similar to individuals with AD, the higher mortality in individuals with UNS was observed solely with atypical APD usage. In individuals with VaD and Mixed, both atypical and typical APDs were linked to an increased risk of mortality. In individuals with VAD, we found nonsignificant trends showing an increased risk of mortality for typical APD use compared to atypical APD usage. In individuals with LBD, we found nonsignificant trends indicating an increased risk of death for typical APD use compared to atypical use and no APDs at all.

General comment

Previous research has highlighted concerns regarding the usage of APDs, which are primarily used to alleviate BPSD.[6-7] Numerous studies have shown that APD therapy in individuals with dementia can have major negative effects, including death.[15] Furthermore, it is unclear if APD use contributes considerably to the improvement of BPSD. An RCT of individuals with AD found that olanzapine and risperidone had a clear favorable impact in alleviating BPSD when compared to placebo and quetiapine.[21] However, the advantages were only shown in those who were able to tolerate the drugs. We observed that APDs are associated with an increased risk of mortality in individuals with dementia. Several reasons have been proposed to explain why APD therapy increases mortality. Generally, atypical APDs, which occupy Dopamine D2 receptors only transiently are thought to be associated with lower risk of EPS.[40] However, when the dosage of APDs is taken into account, atypical antipsychotics are no safer than traditional antipsychotics in terms of development of Parkinsonism.[41] Furthermore, cardio- and cerebrovascular events have been documented as a significant adverse effect of APD therapy.[42] High rates of ventricular arrhythmias and cardiac arrest have been linked to typical APDs,[43] whereas atypical APDs have been linked to high rates of venous thromboembolism. [44] Both typical and atypical APDs have been associated with QT prolongation.[45] Studies suggest that whether the benefits of APDs outweigh the risks depends on the unique profile of the individual, which includes the specific BPSD characteristics and dementia severity.[22] Following this, our findings point to the need for caution while prescribing APDs to individuals with dementia.

6.4 GUN OWNERSHIP IN INDIVIDUALS WITH DEMENTIA (STUDY 4)

In our cohort, 3.4% of individuals with dementia owned a firearm and one in five of them was considered unsuitable for its possession. However, a high percentage of individuals lacked information on firearm status. When compared to those who did not have a firearm, firearm owners were more likely to be younger, male, and live alone without the support of home care. Additionally, 23% of these individuals had a moderate severe or very severe dementia. Furthermore, even though the overall use of psychiatric medication was slightly lower in this group, 4% of persons with firearm used antipsychotic medication, 10% hypnotics and 24% antidepressants. Finally, living arrangement, dementia subtype, diagnostic unit, APD, hypnotics prescription, MMSE score, and gender were the most significant predictors of being reported to the police as unsuitable to own a firearm in SveDem.

General comment

Our findings suggest that individuals with dementia who possess a firearm are more independent and have better overall health, suggesting that they may still be able to safely use a firearm. However, several of these individuals had dementia that was either moderately severe or extremely severe. Furthermore, the general usage of psychiatric medicine indicates that psychiatric symptoms may be present in this group as well. It is difficult to assess a competence to handle a firearm in someone who has just been diagnosed with dementia. Removing the firearm automatically when a person is diagnosed with dementia may promote social isolation and threaten the individual's personhood. In Sweden, a combination of variables (type of dementia diagnosis, gender, severity of cognitive impairment, psychiatric medication, living arrangement) are considered when deciding whether or not to remove the firearm. However, our findings, as well as those of others, indicate that the subject of firearm status may be rarely raised in clinical settings.212–214 We suggest that the date of firearm retirement should be addressed in advance between individuals with dementia, their family members, and healthcare practitioners and individuals with dementia should take an active part in this decision. This manner, individuals with dementia's and their surrounding’s safety may be ensured without jeopardizing their ability to make their own decisions.

6.5 METHODOLOGICAL LIMITATIONS AND BIASES

A valid study is the one with a low systematic error in estimations, typically referred to as biases. Internal validity reflects the validity of the conclusions derived in relation to members of the source population. There are three main components of internal validity: confounding, selection bias, and information bias.[215]

Confounding bias

Confounding bias can be thought of as a conflation mix-up of effects.[215] The influence of extraneous elements is mistaken for – or combined with – the real exposure effect, causing the apparent effect of the exposure of interest to be skewed. A confounding factor can cause significant distortion, leading to an overestimation or underestimation of an effect or affecting its direction. To be deemed a confounder, a variable must be linked to both the study's exposure and the outcome. In Studies 1 and 2, we did not have access to a number of possible confounding sources. Comorbidities, for example, are not recorded in the registries we utilized, thus they could not be accounted for in the studies. Furthermore, since there was no information regarding dementia severity at the time of enrollment in the BPSD registry, we utilized cognitive data (MMSE) at the time of dementia diagnosis, as well as the period between these two time points, as a proxy for severity. Additionally, MMSE score may be viewed as both a confounder and an intermediate factor in the BPSD study: on the one hand, MMSE score is one of the factors used to determine the diagnosis and hence has an impact on the diagnosis; on the other hand, MMSE score is used as a proxy for the pathogenic component that underpins the diagnosis-BPSD association.

In Study 3, individuals who have been prescribed APDs differed considerably from those who have not been prescribed APD. They were more frail and more likely to reside in long-term care facilities. To address this issue, we modified our model to account for group differences. However, we cannot rule out the possibility that additional confounding variables that were not measured in the registries could have biased our findings and led to an overestimation of the association between APD and mortality. Other uncontrolled confounders, such as BPSD, may potentially be present in this study. BPSD, for which APD is prescribed, is linked to a higher death rate and may be a significant confounder in the relationship. However, we were unable to include them in the model. As a result, it is possible that the true association between APD and death is weaker than the one we observed.

Selection bias

Selection biases are errors that occur as a result of subject selection methods and other factors that impact participation in a study.[215] The relationship between exposure and disease is different for those who participate and all those who should have been theoretically eligible for investigation, including those who do not participate. Therefore, the associations identified in research represent a combination of variables that determine participation and forces that determine disease incidence since estimates of effects are conditioned on participation. Selection bias usually happens at the first stages of a study, when patients are recruited, or later in the research, when patients are lost during follow-up. As a result of the selection bias effect, the estimate obtained from the research participants differs from the estimate obtainable from the target population.

In 2020, the SveDem coverage of incident dementia cases was expected to be 43%,[166] while the BPSD registry coverage of patients with dementia residing in nursing homes was estimated to be about 40%.[173] It is unclear how the individuals who participate in SveDem and BPSD vary from those who have not. The individuals in quality registers were shown to be healthier, receive better quality of care and have lower risk of death, skewing the generalizability towards this pattern.[216] In Study 1-2, more troublesome BPSD like hyperactivity could be one of the reasons for moving a person with dementia to a long-term care facility. Therefore, in our studies, their frequency could be overestimated and the results cannot be generalized to individuals with dementia living in a community. The majority of gun owners in Study 4 live in northern Sweden, which is underrepresented in SveDem. As a result, the study's total number of individuals owning a firearm may be underestimated. The non-responders may differ in several characteristics in comparison to persons included in the study and therefore affect the estimation. Furthermore, individuals in these areas may be diagnosed more often in primary clinics rather than memory clinics, which might lead to additional biases in selection. Individuals in primary care are older, have slightly fewer neuropsychological examinations, less CT or MR scanning and are more likely to receive diagnosis of UNS.[166]

Information bias

Information bias refers to measurement inaccuracies in exposure, confounders or outcomes.[215] In the case of discrete variables, measurement error is commonly referred to as classification error or misclassification.

Dementia diagnosis in SveDem is based on clinical criteria. Clinical diagnosis has a lower overall sensitivity than the neuropathological examination. Nonetheless, diagnoses made at baseline in SveDem are seldom modified.[217] In Study 3, we used data from the SPDR about the filled prescriptions. The identification of people who fill prescriptions is not always the same as the identification of those who actually take the medicine. This bias might cause the effect to be overestimated. Another sort of misclassification bias known as "recall bias" may have had an impact on the results in Study 1, 2 and 4. For example, caregivers may find it easier to recall more stressful symptoms that lead to increased burden, resulting in an overestimation of their frequency. Given the self-reporting nature of the firearm ownership status in Study 4, it is likely that some people opted to conceal this information or were unable to recollect it due to cognitive decline.

7 CONCLUSIONS

7.1 GENERAL CONCLUSIONS

Individuals with dementia who live in long-term care facilities frequently develop BPSD. Despite the fact that our sample included variety of dementia diagnoses, they all had a high frequency of irritability, aberrant motor behavior and agitation/aggression. We also observed a high frequency of unmet needs, the most prevalent of which were pain, sleeping problems, impaired hearing and vision. In each dementia type, there was a positive association between the number of unmet needs and BPSD. Individuals with dementia are prescribed both typical and atypical APDs. Their usage, however, was associated with an increased risk of mortality. In our study, 3.4% of individuals with owned a firearm. Gun owners were younger men who were still living more independent lives. The decision to remove the firearm was not made solely on the basis of a dementia diagnosis, but a combination of factors was considered.

7.2 SPECIFIC CONCLUSIONS

1. BPSD is common among individuals with dementia residing in long-term care facilities with 75% of all individuals exhibiting at least one clinically significant BPSD.
2. Amongst all symptoms, aberrant motor behaviour, agitation and irritability were the most frequent, occurring commonly in all dementias.
3. Despite the fact that the individuals in our sample had various dementia diagnoses, we found similarities in the type of their symptoms.
4. Unmet needs are commonly present in individuals with dementia.
5. In the entire cohort, pain was the most prevalent unmet need, followed by sleeping disturbances and impaired hearing and impaired vision.
6. BPSD increases in the presence of physical or psychological unmet needs, regardless of the type of dementia.
7. Use of APDs at the time of dementia diagnosis was associated with increased mortality risk in individuals with AD, Mixed, UNS, and VaD.
8. Higher risk for mortality was found with typical APDs in individuals with Mixed and VaD.
9. Atypical APDs were related with higher risk for mortality in individuals with AD, Mixed, UNS, and VaD.

10. Of all individuals included in the study, 3.4% owned a firearm, of whom 22.2% were reported as unsuitable to own it.
11. Almost one-fifth of individuals included in the study lacked information on their firearm status.
12. When deciding whether or not to remove the firearm, physicians take a number of criteria into consideration, including the type of dementia diagnosis, gender, level of cognitive impairment, psychiatric medication, and living arrangements.

8 POINTS OF PERSPECTIVE

…that is, who authored the painting on the cover of this Thesis?

Diagnostic systems that classify symptoms improve the understanding of mental illness and help its treatment.[218] Moreover, formal diagnosis provides an explanation for the symptoms and thereby may decrease the anxiety caused by unknown cognitive problems - both among patients and their caregivers.[219] A formal diagnosis also may increase the sense of control over the course of the disease and can promote finding ways of adjusting to the changes experienced.[2] However, diagnosis can be also seen as a label that triggers cognitive processes of stereotypization.[218] Stereotypes are knowledge structures that are learned by most members of a cued social group.[220] Individuals with a label (diagnosis) are perceived within the frame of a stereotype, as homogeneous and that their traits are stable (not subject to change or influence of the environment). This prevents recognition of the idiosyncratic characteristics of each patient and impedes a comprehensive understanding of their behavior. For this reason, receiving the diagnosis carries the risk of stigmatization and marginalization of people with mental illness. Perhaps the most striking example of stigmatization associated with diagnosis is a pathologization of the behavior of individuals with dementia. Dementia is commonly interpreted as a partial or complete loss of self, until "*there is nothing left*".[80] Following this, the behavior of the person who has "lost self" is treated as lacking internal locus of control or intentionality, and therefore labelled as disorganized or abnormal.

Although not explicitly stated, this interpretation of dementia is embedded in the prevalent in dementia research a Cartesian perception of the relationship between mind and body. Descartes effectively separated mind and body in the seventeenth century, with the mind taking precedence over the body. While the mind is considered to be the most important aspect of selfhood, the Cartesian dualism implies that the body is fundamentally passive. Therefore, the widely held belief that cognitive decline entails a loss of selfhood has philosophical roots. In this view, the existential degradation of selfhood associated with Alzheimer's disease is, to a considerable measure, the outcome of a philosophical heritage, rather than just neuropathology.

Thus, the idea of selfhood in dementia is strictly bound to Cartesian perception of the dualisms of mind and body. In the case of persons with dementia, it is a body that takes control over a disrupted mind. In western culture, self is equated with cognitive mind and this is reflected in the scientific discourse around dementia, currently dominated by the biomedical model. The

biomedical model focuses exclusively on pathological brain changes occurring in dementia, and overlooks the contribution of external factors to the emergence of BPSD. Moreover, although there were attempts to create comprehensive models of BPSD,[34] discussions about personality changes are not embedded in any psychological theories of personality or emotions.

Kales and colleagues' model resembles the personality system suggested in 1995 by Mischel and Shoda.[221] According to their cognitive-affective system of personality, the behavior of a person can be predicted from a comprehensive understanding of the person, the situation, and the interaction between person and situation.[221] In contrast to the conceptions of personality as dispositions, behavior emerges from the individual's perception of themselves in a particular situation. People can be characterized by the stable patterns of behaving differently in various situations. From this perspective, it is important to see the context in which the behavior occurs. Aggressive behavior can be a reaction to bathing and result from misunderstanding the situation as threatening. It is possible that the behavior would not appear in a different context. The perception of the situation can be influenced both by the external factors (e.g. behavior of caregiver, relation to caregiver) and factors associated with the patient themselves (e.g. type and severity of neurodegeneration).

The underlying philosophy employed by researchers of causes of behavior has important implications in the perception of the behavior of the individual, and consequently translates into research questions and the framing of hypotheses. This has further consequences in treatment and decisions about implementing pharmacological intervention. The exclusion of a psychological perspective in explaining BPSD may come from the notion that neurodegeneration overrides individual differences. Although this can be true in some cases, different studies conclude that the role of environment, caregivers and premorbid personality seem to contradict this conception.[6]

Therefore, it seems that there is a need for a new framework to approach behavior of persons with dementia. In the embodied selfhood framework, the quest for selfhood of the person affected by dementia is given priority.[80] To this end, researchers look for "selfhood beyond cognition". This emerging perspective integrates Merleau-Ponty's understanding of non-representational intentionality and the primordial body with Bourdieu's idea of habitus,[9] which connects bodily dispositions to social world structures.[222–224] The most significant aspect of Merleau-Ponty's perspective is the idea that there is a fundamental level of existence that does not include a cognitive form of awareness.[9] As a result, the pre-reflective body is directed toward the world without the need for a reflective comprehension of how it is directed. In her

ethnographic studies, Kontos (2004) gives the following example of such an approach describing one of the participants of her study passing the doorway: "…*just as we all go through a doorway without checking the width of the doorway against that of our body. This was evidenced by the recognizable fluidity to their gait: it had not become, as a result of the walker, a sequence of partial movements strung laboriously together. Clearly, they were not pausing to evaluate the respective measurements of their walker and the space to be navigated."*[225] From this perspective, selfhood is found in the existential expressiveness of the body that arises from our ability to act, the know-how of a person whose primary relationship to the environment is one of pre-reflection, action, and practical engagement.[80,222] Bourdieu, on the other hand, claims that the conditioning connected with membership in a certain social class, through one's relationship to one's own body, tends to inculcate in persons' tendencies and generative schemes for being and seeing, which he refers to as habitus.[223,224] To put it another way, habitus is a way of being that is embodied in humans and turned into motor schemes and bodily automatisms, which manifest as postures, gestures, and motions.

Altogether, according to the embodied perspective on selfhood, our selfhood is not limited by the rigid frame dictated by Cartesian dimensionality, but can be found in the way we move, in our gestures and the mimics of our faces. Similarly, persons whose minds were affected by neurodegeneration do not cease to be persons but maintain what constituted the very essence of them in the way they engage with their surroundings. Also, their behavior bears a meaning in a given context and can be a valuable source of information for their relatives and caregivers.

cIf dementia truly equates the destruction of selfhood and disorganized, uninhabited behavior, then who authored the painting on the cover of this Thesis? Marian Siwek, born in 1936, was a Polish artist-outsider who always contested the ruling political system. In his final years, the artist once again excluded himself from public life - this time the cause was Alzheimer's disease. Despite the progression of the disease, Marian Siwek did not stop creating. The soundness and intensity of expression of Marian Siwek's later work, as well as those of others (e.g. William Utermohlen) was an inspiration for this Thesis.

9 ACKNOWLEDGEMENTS

I would like to sincerely thank all the persons who contributed to the realization of this Thesis.

I would like to start with my main supervisor, **Dorota Religa**, for making this Thesis possible. I am thankful for the opportunity to pursue my PhD studies with her group and all the support I received during those years. Most importantly, thank you sharing your knowledge with me and the independence you provided me with in realizing my projects.

I would also like to express my gratitude for my co-supervisors:

Katarina Nägga for her useful insight into the BPSD-registry and for all of our discussions throughout the writing of the articles. I'm also grateful for your patience with my tendency for making silly mistakes and overlooking details.

Joana Braga Pereira for believing in me despite my numerous errors and tendency for getting distracted. Your dedication and love for science have always been an inspiration to me.

Maria Eriksdotter for guiding me thorough the registry-based research. Your insightful remarks and constructive discussions during SveDem meetings were beneficial to my understanding of SveDem and scientific development.

Bengt Winblad, thank you for your unwavering support during my PhD and constantly pushing me to improve and work harder. It was always an honor (and pleasure) to discuss science with you.

I'd also like to express my gratitude to my mentor, **Birgitta Ausen**, for her calm presence that always made me feel that everything is ok. I have always valued your opinion and appreciated your dedication to mentoring. Meeting you was always a pleasure.

Maria Ankarcrona and **Eric Westman** for the great working environment at NVS and the division of Clinical Geriatrics. **Gunilla Johannson**, **Anette Eidehall**, **Catarina Cleveson**, **Sofia Fridén** and **Camille Birgegård**, for all your support throughout my studies.

Martin and Alfred for great IT support; for always dropping by when passing by our corridor and not falling asleep during our dissertations (against all odds!).

I would also like to thank everyone from the SveDem group:

My great thanks to my friend and colleague **Juraj**. We had lots of fun together making all kinds of mistakes. I am happy we went through this adventure together! **Sara** for all your help, enormous dedication to science and your patients, and tons of new ideas. **Hong** for always being there to help and support me; **Tuan** for being a great office mate and **Pavla** for introducing me to the group. **Eva, Irena, Ana and Bojana,** our guests from Slovenia. It has

always been fun to have you here. **Karin Westling**, **Ann-Katrin Edlund** and **Emma Timerdal**, for your work on SveDem and always being ready to help us.

I would also like thank **RADAR-AD team**: **Casper de Boer** and **Marijn Muurling** for being always ready to help us; **Krister** for dedication to the project and working hard on improving my Swedish pronunciation; **Göran** for helping us with tests; **Marie R.** and **Sara** for helping us with the recruitment; **Olle.**.. one day it will all work, don't worry! Finally, I'd want to thank all of the participants who have committed their time and effort to help us realize this project.

My special thanks go to all the awesome people at NVS (in chronological or thematic order):

Soheil for your free spirit, love for ice-cream and always believing in me! **Medoune** for being my friend, and asking me this very important question: *Why do you even care?!;* **Axel** for being this incredible human being with a rare distant to life and sense of humor. For great pep talks while I was running on a treadmill ("*XXXX X€%%&!!!!")** **removed because of racist or inappropriate content;** **Jessy** for bringing music back to my life**; Julen** for explaining me why excuses are like asses, all the great history we had in Vårberg and our long runs; **Maria L.** for somehow making me feel that it is ok to be the person I am (it may sounds weird but you do make me feel this way); **Dani** for being this big metal guy with a heart of a fluffy teddy bear**; Raul** for all life lessons ("*Never run for the train, there will be another one");* **Laetitia** for your big heart, all your emotions, and Saturdays in Neo☺**; Elena** for the voice of common sense in this craziness and partying with 80 years old seniors☺; **Simone** for being this great, proud and passionate person. Let's have a fika soon? **Bernie** for your smiling face (even when you feel sad) yoga and self-development talks; **Helen** for the unique person you are, sense of humor and digressions; **Hazal** for fun-loving and strength; **Lorena** for the concert we went together and concerts we will go to; **Chenhing** for being a great and rare type of person. I am always super happy when I meet you!!; **Konstantinos** for constant support, telling me that I look fit, and inspiring sailing stories; **Ipsit, Amit, Mona, Ceren**, **Nuno, Giacomo, Francesca, Andrea, Luis, Arturo, Vilma, Una, Oihan** and **Alastair** for the time we spent together, parties and sometimes strange chats. **Xin Xuan, Joao, Quim**, **Shambhu** making my first year in Sweden so special!

Mite for your patience, physic-based psychotherapy, unique attitude to life, good coffees when we have something to celebrate, or we fail, or because nothing is happening; **Anna C.** for your passion to life, genuineness and teaching me how to save money; **Daniel** for your strange ability to blend in with the office; **Marina** for the spa bus and a valuable contribution to the work of the bus committee; **Magali** for the life changing discussion during the early morning bus rides and for your dedication to the work in the bus committee; **Gosia** for proving that smiling doesn't mean being weak – you can be a strong and nice person in the same time!

Renata for your work ethic, strong personality and all the hikes - Nacka will never get boring!: **Peter** for your sensitivity and the great birthday ever☺; **Andrei** the past and future hikes and for your passion for DAGs.

Nira, Caroline, Patri, Lissett, Annegret, Anna I-P, Gulia, Rosaleena, Gustav, Kosta, Anna R., Sophia and Shayan: although we didn't have a chance to spend much time together, you are all great co-workers and lunch mates.

I would never send this Thesis to printing without acknowledging my friends outside KI and Sweden.

Anna for making me feel accepted even when I was writing the Thesis or having silly problems. For long coffees at Organico, for always ordering gluten free plant beef wraps (they are simply the best!). It is quite difficult to write all reasons why I am so happy to have you in my life so I will just thank you for showing me that it is possible to find a best friend even when you are so old and so far away from your home and culture.

Matthias for our bike rides to Flembo, passionate discussions about the concept of "Nation" and piano-flute duets. Most importantly, for being a great and caring friend, being always there to support me without asking for anything in return.

Guto a.k.a sexy sax man for showing me that music is not about exams, performance and perfection but that actually something to enjoy. For your commitment as a teacher and support as a friend. Also, for telling me that this is in their 30. when women start being really attractive.

Moj doktorat nigdy by nie powstał bez wsparcia mojej rodziny i przyjaciół. Przede wszystkim mojej mamy, **Moniki**, która zawsze wierzyła, że coś ze mnie będzie i nigdy się nie poddała; mojego taty, **Pawła**, który zawsze ma świetne pomysły na grant; moich braci – **Tomka** i **Kuby** – bez których generalnie byłoby słabo.

Zawsze mogłabym liczyć na wsparcie moich najlepszych w świecie przyjaciół, a dokładniej **Wyraka**, który zainwestował majątek w moja edukację i ciągle czeka na zysk; **Kasi**, która inwestuje majątek w Wyraka i ciągle czeka na zysk; **Manushki**, która może kiedyś znajdzie odpowiednie miejsce na bunkier, bo jak przyjdzie wojna, to dalej trzeba będzie płacić ratę za mieszkanie ale trudno powiedzieć, bo w sumie nie ma precedensu; **Mateusza**, rozpoznawalnej w Krakowie gwiazdy punk rocka, który gra na festiwalach, i nawet w Warszawie; naczelnego Vege Runners **Pająka,** który nieustannie i bez zmęczenia rozwija big biznes, uzupełniając asortyment sklepu Vege Runners coraz to nowymi wzorami kapuścianych koszulek; hakera i znanego łamacza internetowych serc **Radka C.,** który, od wspólnego mieszkania, już zawsze sprząta, bo zobaczył, jak to jest, kiedy mieszka się z kimś, kto nie sprząta; **Asi M.** której wrażliwość, zawsze była dla mnie inspiracja, **Asi B.**, która jest moja przyjaciółka pomimo tego, ze zna mnie już 26 lat!!!; **Justynie K**, przyjaciółce oraz sezonowej współpracowniczce z młodosci, która zawsze potrafi rozbawić otoczenie ciekawymi historiami, np. tymi o narożniczku; **Paulinie Sz**, z którą praca z finometrem przekształciła się w przyjaźń…w końcu nic tak nie zbliża, jak potrzeba domknięcia☺

Chciałabym także podziękować **Michałowi K**. i **Joasi P**., moim opiekunom pracy magisterskiej z Uniwersytetu Jagiellońskiego w Krakowie, którzy wprowadzili mnie w świat badań i nauki. Praca z Wami zawsze była ekscytująca, trochę dziwna, a przede wszystkim super fajna i fascynująca!

Finally, I'd want to express my gratitude for all of the funds that enabled me to do this research: Gun och Bertil Stohnes Stiftelse, CIMED grant, Alzheimerfonden, Swedish Brain Foundation, and Margaretha af Ugglas' foundation and Swedish Research Council and by grants provided by the Stockholm County Council (ALF project) and Radar-AD project.

10 REFERENCES

1. Lyketsos CG, Carrillo MC, Ryan JM, et al. Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dement*. 2011;7(5):532-539. doi:10.1016/j.jalz.2011.05.2410

2. Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. *Allg Zschr Psychiatr Psych Gerichtl Med*. 1907;64:146-148.

3. Hippius H. The discovery of Alzheimer's disease. *Dialogues Clin Neurosci*. 2003;5(1):101-108. doi:10.31887/DCNS.2003.5.1/hhippius

4. International Psychiatric Association (IPA) Complete Guides to Behavioural and Psychological Symptoms of Dementia. Published online Revised 2015 1996. https://www.ipa-online.org/publications/guides-to-bpsd

5. Finkel SI, Burns A. BPSD Consensus Statement, International Psychogeriatric Association. Published online 1999.

6. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and Psychological Symptoms of Dementia. *Front Neurol*. 2012;3. doi:10.3389/fneur.2012.00073

7. Kimiko Konishi KH, Masayuki Tani HT. Mood Symptoms are Related to Psychotic Symptoms in Severe Alzheimer?s Disease. *J Addict Res Ther*. 2011;s5. doi:10.4172/2155-6105.S5-002

8. Helvik AS, Selbæk G, Šaltytė Benth J, Røen I, Bergh S. The course of neuropsychiatric symptoms in nursing home residents from admission to 30-month follow-up. Rajji TK, ed. *PLOS ONE*. 2018;13(10):e0206147. doi:10.1371/journal.pone.0206147

9. Brodaty H, Draper B, Saab D, et al. Psychosis, depression and behavioural disturbances in Sydney nursing home residents: prevalence and predictors. *Int J Geriatr Psychiatry*. 2001;16(5):504-512. doi:10.1002/gps.382

10. Yoro-Zohoun I, Nubukpo P, Houinato D, et al. Neuropsychiatric symptoms among older adults living in two countries in Central Africa (EPIDEMCA study). *Int J Geriatr Psychiatry*. 2019;34(1):169-178. doi:10.1002/gps.5006

11. Slachevsky A, Budinich M, Miranda-Castillo C, et al. The CUIDEME Study: Determinants of Burden in Chilean Primary Caregivers of Patients with Dementia. *J Alzheimers Dis*. 2013;35(2):297-306. doi:10.3233/JAD-122086

12. Haibo X, Shifu X, Pin NT, et al. Prevalence and severity of behavioral and psychological symptoms of dementia (BPSD) in community dwelling Chinese: findings from

the Shanghai three districts study. *Aging Ment Health*. 2013;17(6):748-752. doi:10.1080/13607863.2013.781116

13. Majer R, Simon V, Csiba L, Kardos L, Frecska E, Hortobágyi T. Behavioural and psychological symptoms in neurocognitive disorders: Specific patterns in dementia subtypes. *Open Med*. 2019;14(1):307-316. doi:10.1515/med-2019-0028

14. Selbæk G, Kirkevold Ø, Engedal K. The prevalence of psychiatric symptoms and behavioural disturbances and the use of psychotropic drugs in Norwegian nursing homes. *Int J Geriatr Psychiatry*. 2007;22(9):843-849. doi:10.1002/gps.1749

15. Huang SS, Wang WF, Liao YC. Severity and prevalence of behavioral and psychological symptoms among patients of different dementia stages in Taiwan. *Arch Clin Psychiatry São Paulo*. 2017;44(4):89-93. doi:10.1590/0101-60830000000127

16. Paddick SM, Kisoli A, Longdon A, et al. The prevalence and burden of behavioural and psychological symptoms of dementia in rural Tanzania: Behavioural and psychological symptoms of dementia in Africa. *Int J Geriatr Psychiatry*. 2015;30(8):815-823. doi:10.1002/gps.4218

17. Zuidema SU, Derksen E, Verhey FRJ, Koopmans RTCM. Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. *Int J Geriatr Psychiatry*. 2007;22(7):632-638. doi:10.1002/gps.1722

18. McCarthy JF, Blow FC, Kales HC. Disruptive Behaviors in Veterans Affairs Nursing Home Residents: How Different Are Residents with Serious Mental Illness?: DISRUPTIVE BEHAVIORS IN VA NURSING HOMES. *J Am Geriatr Soc.* 2004;52(12):2031-2038. doi:10.1111/j.1532-5415.2004.52559.x

19. Allegri RF, Sarasola D, Serrano CM, et al. Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease. *Neuropsychiatr Dis Treat.* 2006;2(1):105-110.

20. Brodaty H, Donkin M. Family caregivers of people with dementia. *Dialogues Clin Neurosci.* 2009;11(2):217-228.

21. van der Linde RM, Stephan BCM, Dening T, Brayne C. Instruments to measure behavioural and psychological symptoms of dementia: BPSD instruments. *Int J Methods Psychiatr Res*. 2014;23(1):69-98. doi:10.1002/mpr.1414

22. Cummings JL. The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology*. 1997;48(Issue 5, Supplement 6):10S-16S. doi:10.1212/WNL.48.5_Suppl_6.10S

23. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-2308. doi:10.1212/WNL.44.12.2308

24. Cummings J. The Neuropsychiatric Inventory: Development and Applications. *J Geriatr Psychiatry Neurol*. 2020;33(2):73-84. doi:10.1177/0891988719882102

25. Lai C. The merits and problems of Neuropsychiatric Inventory as an assessment tool in people with dementia and other neurological disorders. *Clin Interv Aging*. Published online July 2014:1051. doi:10.2147/CIA.S63504

26. McKinlay A, Grace RC, Dalrymple-Alford JC, Anderson TJ, Fink J, Roger D. Neuropsychiatric problems in Parkinson's disease: Comparisons between self and caregiver report. *Aging Ment Health*. 2008;12(5):647-653. doi:10.1080/13607860802343225

27. Wood S, Cummings JL, Hsu MA, et al. The Use of the Neuropsychiatric Inventory in Nursing Home Residents: Characterization and Measurement. *Am J Geriatr Psychiatry*. 2000;8(1):75-83. doi:10.1097/00019442-200002000-00010

28. Cohen-Mansfield J. Nonpharmacologic Interventions for Inappropriate Behaviors in Dementia: A Review, Summary, and Critique. *Am J Geriatr Psychiatry*. 2001;9(4):361-381. doi:10.1097/00019442-200111000-00005

29. Hancock GA, Woods B, Challis D, Orrell M. The needs of older people with dementia in residential care. *Int J Geriatr Psychiatry*. 2006;21(1):43-49. doi:10.1002/gps.1421

30. Cohen-Mansfield J, Dakheel-Ali M, Marx MS, Thein K, Regier NG. Which unmet needs contribute to behavior problems in persons with advanced dementia? *Psychiatry Res*. 2015;228(1):59-64. doi:10.1016/j.psychres.2015.03.043

31. Kovach CR, Noonan PE, Schlidt AM, Wells T. A Model of Consequences of Need-Driven, Dementia-Compromised Behavior. *J Nurs Scholarsh*. 2005;37(2):134-140. doi:10.1111/j.1547-5069.2005.00025_1.x

32. Algase DL, Beck C, Kolanowski A, et al. Need-driven dementia-compromised behavior: An alternative view of disruptive behavior. *Am J Alzheimers Dis*. 1996;11(6):10-19. doi:10.1177/153331759601100603

33. Smith M, Gerdner LA, Hall GR, Buckwalter KC. History, Development, and Future of the Progressively Lowered Stress Threshold: A Conceptual Model for Dementia Care: PLST REVIEW. *J Am Geriatr Soc*. 2004;52(10):1755-1760. doi:10.1111/j.1532-5415.2004.52473.x

34. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350(mar02 7):h369-h369. doi:10.1136/bmj.h369

35. Levy R, Dubois B. Apathy and the Functional Anatomy of the Prefrontal Cortex–Basal Ganglia Circuits. *Cereb Cortex*. 2006;16(7):916-928. doi:10.1093/cercor/bhj043

36. Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behavior. *Dialogues Clin Neurosci*. 2007;9(2):141-151.

37. Lanari A, Amenta F, Silvestrelli G, Tomassoni D, Parnetti L. Neurotransmitter deficits in behavioural and psychological symptoms of Alzheimer's disease. *Mech Ageing Dev*. 2006;127(2):158-165. doi:10.1016/j.mad.2005.09.016

38. Reeves S, Brown R, Howard R, Grasby P. Increased striatal dopamine (D2/D3) receptor availability and delusions in Alzheimer disease. *Neurology*. 2009;72(6):528-534. doi:10.1212/01.wnl.0000341932.21961.f3

39. Engelborghs S, Vloeberghs E, Le Bastard N, et al. The dopaminergic neurotransmitter system is associated with aggression and agitation in frontotemporal dementia. *Neurochem Int*. 2008;52(6):1052-1060. doi:10.1016/j.neuint.2007.10.018

40. Cummings JL, Kaufer D. Neuropsychiatric aspects of Alzheimer's disease: The cholinergic hypothesis revisited. *Neurology*. 1996;47(4):876-883. doi:10.1212/WNL.47.4.876

41. Löppönen MK, Isoaho RE, Räihä IJ, et al. Undiagnosed Diseases in Patients with Dementia – A Potential Target Group for Intervention. *Dement Geriatr Cogn Disord*. 2004;18(3-4):321-329. doi:10.1159/000080126

42. Hodgson NA, Gitlin LN, Winter L, Czekanski K. Undiagnosed Illness and Neuropsychiatric Behaviors in Community Residing Older Adults With Dementia: *Alzheimer Dis Assoc Disord*. 2011;25(2):109-115. doi:10.1097/WAD.0b013e3181f8520a

43. Caspi E, Silverstein NM, Porell F, Kwan N. Physician outpatient contacts and hospitalizations among cognitively impaired elderly. *Alzheimers Dement*. 2009;5(1):30-42. doi:10.1016/j.jalz.2008.05.2493

44. Miller J. To treat or not to treat: managing bacteriuria in elderly people. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2001;164(5):619-620.

45. Walker S, McGeer A, Simor AE, Armstrong-Evans M, Loeb M. Why are antibiotics prescribed for asymptomatic bacteriuria in institutionalized elderly people? A qualitative study of physicians' and nurses' perceptions. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2000;163(3):273-277.

46. Limpawattana P, Phungoen P, Mitsungnern T, Laosuangkoon W, Tansangworn N. Atypical presentations of older adults at the emergency department and associated factors. *Arch Gerontol Geriatr*. 2016;62:97-102. doi:10.1016/j.archger.2015.08.016

47. Slaughter SE, Eliasziw M, Morgan D, Drummond N. Incidence and predictors of eating disability among nursing home residents with middle-stage dementia. *Clin Nutr*. 2011;30(2):172-177. doi:10.1016/j.clnu.2010.09.001

48. Abengaña J, Chong MS, Tay L. Delirium superimposed on dementia: phenomenological differences between patients with and without behavioral and psychological symptoms of dementia in a specialized delirium unit. *Int Psychogeriatr*. 2017;29(3):485-495. doi:10.1017/S1041610216001836

49. Ballard C, Smith J, Corbett A, Husebo B, Aarsland D. The role of pain treatment in managing the behavioural and psychological symptoms of dementia (BPSD). *Int J Palliat Nurs*. 2011;17(9):420-424. doi:10.12968/ijpn.2011.17.9.420

50. Kunik ME, Snow AL, Davila JA, et al. Causes of Aggressive Behavior in Patients With Dementia. *J Clin Psychiatry*. 2010;71(09):1145-1152. doi:10.4088/JCP.08m04703oli

51. Lukas A, Schuler M, Fischer TW, et al. Pain and dementia: A diagnostic challenge. *Z Für Gerontol Geriatr*. 2012;45(1):45-49. doi:10.1007/s00391-011-0272-4

52. Massimo L, Kales HC, Kolanowski A. State of the Science: Apathy As a Model for Investigating Behavioral and Psychological Symptoms in Dementia: Apathy in dementia. *J Am Geriatr Soc*. 2018;66:S4-S12. doi:10.1111/jgs.15343

53. Roth HL. Dementia and Sleep. *Neurol Clin*. 2012;30(4):1213-1248. doi:10.1016/j.ncl.2012.08.013

54. Stroud JM, Steiner V, Iwuagwu C. Predictors of depression among older adults with dementia. *Dementia*. 2008;7(1):127-138. doi:10.1177/1471301207084373

55. Bassiony MM, Steinberg MS, Warren A, Rosenblatt A, Baker AS, Lyketsos CG. Delusions and hallucinations in Alzheimer's disease: prevalence and clinical correlates. *Int J Geriatr Psychiatry*. 2000;15(2):99-107. doi:10.1002/(sici)1099-1166(200002)15:2<99::aid-gps82>3.0.co;2-5

56. Phan SV, Osae S, Morgan JC, Inyang M, Fagan SC. Neuropsychiatric Symptoms in Dementia: Considerations for Pharmacotherapy in the USA. *Drugs RD*. 2019;19(2):93-115. doi:10.1007/s40268-019-0272-1

57. Tampi RR, Tampi DJ, Balachandran S, Srinivasan S. Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses. *Ther Adv Chronic Dis*. 2016;7(5):229-245. doi:10.1177/2040622316658463

58. Wongpakaran N, van Reekum R, Wongpakaran T, Clarke D. Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. *Ann Gen Psychiatry*. 2007;6(1):7. doi:10.1186/1744-859X-6-7

59. McCrae RR, Sutin AR. A Five–Factor Theory Perspective on Causal Analysis. *Eur J Personal*. 2018;32(3):151-166. doi:10.1002/per.2134

60. John O, Naumann LP, Soto CJ. Paradigm shift to the integrative big five trait taxonomy: History, measurement, and conceptual issues. In: *Handbook of Personality: Theory and Research*. 3rd ed. Guilford Press; 2008.

61. de Raad B, Mlačić B. *The Lexical Foundation of the Big Five Factor Model*. Vol 1. (Widiger TA, ed.). Oxford University Press; 2015. doi:10.1093/oxfordhb/9780199352487.013.12

62. Costa PT, McCrae RR. Personality in adulthood: A six-year longitudinal study of self-reports and spouse ratings on the NEO Personality Inventory. *J Pers Soc Psychol*. 1988;54(5):853-863. doi:10.1037/0022-3514.54.5.853

63. Roberts BW, DelVecchio WF. The rank-order consistency of personality traits from childhood to old age: A quantitative review of longitudinal studies. *Psychol Bull*. 2000;126(1):3-25. doi:10.1037/0033-2909.126.1.3

64. Mroczek DK, Spiro A. Modeling Intraindividual Change in Personality Traits: Findings From the Normative Aging Study. *J Gerontol B Psychol Sci Soc Sci*. 2003;58(3):P153-P165. doi:10.1093/geronb/58.3.P153

65. Small BJ, Hertzog C, Hultsch DF, Dixon RA. Stability and Change in Adult Personality Over 6 Years: Findings From the Victoria Longitudinal Study. *J Gerontol B Psychol Sci Soc Sci*. 2003;58(3):P166-P176. doi:10.1093/geronb/58.3.P166

66. Roberts BW, Walton KE, Viechtbauer W. Patterns of mean-level change in personality traits across the life course: A meta-analysis of longitudinal studies. *Psychol Bull*. 2006;132(1):1-25. doi:10.1037/0033-2909.132.1.1

67. Allemand M, Zimprich D, Martin M. Long-term correlated change in personality traits in old age. *Psychol Aging*. 2008;23(3):545-557. doi:10.1037/a0013239

68. Terracciano A, Sutin AR. Personality and Alzheimer's disease: An integrative review. *Personal Disord Theory Res Treat*. 2019;10(1):4-12. doi:10.1037/per0000268

69. Robins Wahlin TB, Byrne GJ. Personality changes in Alzheimer's disease: a systematic review. *Int J Geriatr Psychiatry*. 2011;26(10):1019-1029. doi:10.1002/gps.2655

70. Donati A, Studer J, Petrillo S, et al. The Evolution of Personality in Patients with Mild Cognitive Impairment. *Dement Geriatr Cogn Disord*. 2013;36(5-6):329-339. doi:10.1159/000353895

71. Osborne H, Simpson J, Stokes G. The relationship between pre-morbid personality and challenging behaviour in people with dementia: A systematic review. *Aging Ment Health*. 2010;14(5):503-515. doi:10.1080/13607861003713208

72. Low LF, Brodaty H, Draper B. A study of premorbid personality and behavioural and psychological symptoms of dementia in nursing home residents. *Int J Geriatr Psychiatry*. 2002;17(8):779-783. doi:10.1002/gps.697

73. Zielin S, McCabe M. Exploring the Relationship Between Premorbid Personality and Dementia-Related Behaviors. *J Gerontol Nurs*. 2016;42(1):40-48. doi:10.3928/00989134-20151008-77

74. Sutin AR, Stephan Y, Luchetti M, Terracciano A. Self-reported personality traits are prospectively associated with proxy-reported behavioral and psychological symptoms of dementia at the end of life. *Int J Geriatr Psychiatry*. 2018;33(3):489-494. doi:10.1002/gps.4782

75. Tabata K, Saijo Y, Morikawa F, et al. Association of premorbid personality with behavioral and psychological symptoms in dementia with Lewy bodies: Comparison with Alzheimer's disease patients: Premorbid personality and BPSD. *Psychiatry Clin Neurosci*. 2017;71(6):409-416. doi:10.1111/pcn.12511

76. Gilley DW, Wilson RS, Bienias JL, Bennett DA, Evans DA. Predictors of Depressive Symptoms in Persons With Alzheimer's Disease. *J Gerontol B Psychol Sci Soc Sci*. 2004;59(2):P75-P83. doi:10.1093/geronb/59.2.P75

77. Meins W, Frey A, Thiesemann R. Premorbid Personality Traits in Alzheimer's Disease: Do They Predispose to Noncognitive Behavioral Symptoms? *Int Psychogeriatr*. 1998;10(4):369-378. doi:10.1017/S1041610298005468

78. Strauss ME. Premorbid Personality and Behavioral Symptoms in Alzheimer Disease: Some Cautions. *Arch Neurol*. 1997;54(3):257. doi:10.1001/archneur.1997.00550150021010

79. Archer N, Brown RG, Reeves SJ, et al. Premorbid Personality and Behavioral and Psychological Symptoms in Probable Alzheimer Disease. *Am J Geriatr Psychiatry*. 2007;15(3):202-213. doi:10.1097/01.JGP.0000232510.77213.10

80. Kontos PC. Embodied selfhood in Alzheimer's disease: Rethinking person-centred care. *Dementia*. 2005;4(4):553-570. doi:10.1177/1471301205058311

81. Cremers HR, Demenescu LR, Aleman A, et al. Neuroticism modulates amygdala—prefrontal connectivity in response to negative emotional facial expressions. *NeuroImage*. 2010;49(1):963-970. doi:10.1016/j.neuroimage.2009.08.023

82. Deng Y, Li S, Zhou R, Walter M. Neuroticism Modulates the Functional Connectivity From Amygdala to Frontal Networks in Females When Avoiding Emotional Negative Pictures. *Front Behav Neurosci.* 2019;13:102. doi:10.3389/fnbeh.2019.00102

83. Perlman SB, Morris JP, Vander Wyk BC, Green SR, Doyle JL, Pelphrey KA. Individual Differences in Personality Predict How People Look at Faces. Aleman A, ed. *PLoS ONE*. 2009;4(6):e5952. doi:10.1371/journal.pone.0005952

84. PACO group (appendix), Rouch I, Dorey JM, et al. Does Personality Predict Behavioral and Psychological Symptoms of Dementia? Results from PACO Prospective Study. *J Alzheimers Dis*. 2019;69(4):1099-1108. doi:10.3233/JAD-190183

85. Jao YL, Liu W, Williams K, Chaudhury H, Parajuli J. Association between environmental stimulation and apathy in nursing home residents with dementia. *Int Psychogeriatr*. 2019;31(08):1109-1120. doi:10.1017/S1041610219000589

86. Day K, Carreon D, Stump C. The Therapeutic Design of Environments for People With Dementia. *The Gerontologist*. 2000;40(4):397-416. doi:10.1093/geront/40.4.397

87. Marquardt G, Bueter K, Motzek T. Impact of the Design of the Built Environment on People with Dementia: An Evidence-Based Review. *HERD Health Environ Res Des J*. 2014;8(1):127-157. doi:10.1177/193758671400800111

88. Zuidema SU, de Jonghe JFM, Verhey FRJ, Koopmans RTCM. Environmental correlates of neuropsychiatric symptoms in nursing home patients with dementia. *Int J Geriatr Psychiatry*. Published online 2009:n/a-n/a. doi:10.1002/gps.2292

89. Chaudhury H, Cooke HA, Cowie H, Razaghi L. The Influence of the Physical Environment on Residents With Dementia in Long-Term Care Settings: A Review of the Empirical Literature. *The Gerontologist*. 2018;58(5):e325-e337. doi:10.1093/geront/gnw259

90. Zeisel J, Silverstein NM, Hyde J, Levkoff S, Lawton MP, Holmes W. Environmental Correlates to Behavioral Health Outcomes in Alzheimer's Special Care Units. *The Gerontologist*. 2003;43(5):697-711. doi:10.1093/geront/43.5.697

91. Janus SIM, Kosters J, van den Bosch KA, Andringa TC, Zuidema SU, Luijendijk HJ. Sounds in nursing homes and their effect on health in dementia: a systematic review. *Int Psychogeriatr*. 2021;33(6):627-644. doi:10.1017/S1041610220000952

92. Jao YL, Loken E, MacAndrew M, Van Haitsma K, Kolanowski A. Association between social interaction and affect in nursing home residents with dementia. *Aging Ment Health*. 2018;22(6):778-783. doi:10.1080/13607863.2017.1304526

93. Gilhooly KJ, Gilhooly MLM, Sullivan MP, et al. A meta-review of stress, coping and interventions in dementia and dementia caregiving. *BMC Geriatr*. 2016;16(1):106. doi:10.1186/s12877-016-0280-8

94. Cooper C, Balamurali TBS, Livingston G. A systematic review of the prevalence and covariates of anxiety in caregivers of people with dementia. *Int Psychogeriatr*. 2007;19(02):175. doi:10.1017/S1041610206004297

95. Mahoney R, Regan C, Katona C, Livingston G. Anxiety and Depression in Family Caregivers of People With Alzheimer Disease: The LASER-AD Study. *Am J Geriatr Psychiatry*. 2005;13(9):795-801. doi:10.1097/00019442-200509000-00008

96. Huang SS, Lee MC, Liao YC, Wang WF, Lai TJ. Caregiver burden associated with behavioral and psychological symptoms of dementia (BPSD) in Taiwanese elderly. *Arch Gerontol Geriatr*. 2012;55(1):55-59. doi:10.1016/j.archger.2011.04.009

97. Gilmore-Bykovskyi AL, Roberts TJ, Bowers BJ, Brown RL. Caregiver Person-Centeredness and Behavioral Symptoms in Nursing Home Residents With Dementia: A Timed-Event Sequential Analysis. *The Gerontologist*. 2015;55(Suppl 1):S61-S66. doi:10.1093/geront/gnu164

98. Callahan CM, Boustani MA, Unverzagt FW, et al. Effectiveness of Collaborative Care for Older Adults With Alzheimer Disease in Primary Care: A Randomized Controlled Trial. *JAMA*. 2006;295(18):2148. doi:10.1001/jama.295.18.2148

99. Marriott A, Donaldson C, Tarrier N, Burns A. Effectiveness of cognitive–behavioural family intervention in reducing the burden of care in carers of patients with Alzheimer's disease. *Br J Psychiatry*. 2000;176(6):557-562. doi:10.1192/bjp.176.6.557

100. Sorensen S, Pinquart M, Duberstein P. How Effective Are Interventions With Caregivers? An Updated Meta-Analysis. *The Gerontologist*. 2002;42(3):356-372. doi:10.1093/geront/42.3.356

101. Cheng ST, Li KK, Losada A, et al. The effectiveness of nonpharmacological interventions for informal dementia caregivers: An updated systematic review and meta-analysis. *Psychol Aging*. 2020;35(1):55-77. doi:10.1037/pag0000401

102. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. *Nat Rev Dis Primer*. 2015;1(1):15056. doi:10.1038/nrdp.2015.56

103. Maccioni RB, Muñoz JP, Barbeito L. The Molecular Bases of Alzheimer's Disease and Other Neurodegenerative Disorders. *Arch Med Res*. 2001;32(5):367-381. doi:10.1016/S0188-4409(01)00316-2

104. Zhao QF, Tan L, Wang HF, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord*. 2016;190:264-271. doi:10.1016/j.jad.2015.09.069

105. Masters MC, Morris JC, Roe CM. "Noncognitive" symptoms of early Alzheimer disease: A longitudinal analysis. *Neurology*. 2015;84(6):617-622. doi:10.1212/WNL.0000000000001238

106. Román GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. *Lancet Neurol*. 2002;1(7):426-436. doi:10.1016/S1474-4422(02)00190-4

107. Levine DA, Langa KM. Vascular Cognitive Impairment: Disease Mechanisms and Therapeutic Implications. *Neurotherapeutics*. 2011;8(3):361-373. doi:10.1007/s13311-011-0047-z

108. Alosco ML, Spitznagel MB, Cohen R, et al. Reduced cerebral perfusion predicts greater depressive symptoms and cognitive dysfunction at a 1-year follow-up in patients with heart failure: Perfusion, depression, and cognitive function in HF. *Int J Geriatr Psychiatry*. 2014;29(4):428-436. doi:10.1002/gps.4023

109. Liu Q, Zhu Z, Teipel SJ, et al. White Matter Damage in the Cholinergic System Contributes to Cognitive Impairment in Subcortical Vascular Cognitive Impairment, No Dementia. *Front Aging Neurosci*. 2017;9. doi:10.3389/fnagi.2017.00047

110. Tullberg M, Fletcher E, DeCarli C, et al. White matter lesions impair frontal lobe function regardless of their location. *Neurology*. 2004;63(2):246-253. doi:10.1212/01.WNL.0000130530.55104.B5

111. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013;18(9):963-974. doi:10.1038/mp.2013.20

112. Alexopoulos GS. Depression in the elderly. *The Lancet*. 2005;365(9475):1961-1970. doi:10.1016/S0140-6736(05)66665-2

113. Tekin S, Cummings JL. Frontal–subcortical neuronal circuits and clinical neuropsychiatry. *J Psychosom Res*. 2002;53(2):647-654. doi:10.1016/S0022-3999(02)00428-2

114. Chin J, Seo SW, Kim SH, et al. Neurobehavioral Dysfunction in Patients with Subcortical Vascular Mild Cognitive Impairment and Subcortical Vascular Dementia. *Clin Neuropsychol*. 2012;26(2):224-238. doi:10.1080/13854046.2012.658865

115. Staekenborg SS, Su T, van Straaten ECW, et al. Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. *J Neurol Neurosurg Psychiatry*. 2010;81(5):547-551. doi:10.1136/jnnp.2009.187500

116. Gupta M, Khwaja G, Patidar Y, Dasgupta A, Chowdhury D, Batra A. The profile of behavioral and psychological symptoms in vascular cognitive impairment with and without dementia. *Ann Indian Acad Neurol*. 2013;16(4):599. doi:10.4103/0972-2327.120488

117. Fuh JL. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. *J Neurol Neurosurg Psychiatry*. 2005;76(10):1337-1341. doi:10.1136/jnnp.2004.056408

118. McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the Consortium on DLB International Workshop. *J Alzheimers Dis*. 2006;9:417-423.

119. Chiu MJ, Chen TF, Yip PK, Hua MS, Tang LY. Behavioral and Psychologic Symptoms in Different Types of Dementia. *J Formos Med Assoc*. 2006;105(7):556-562. doi:10.1016/S0929-6646(09)60150-9

120. Borroni B, Agosti C, Padovani A. Behavioral and psychological symptoms in dementia with Lewy-bodies (DLB): Frequency and relationship with disease severity and motor impairment. *Arch Gerontol Geriatr*. 2008;46(1):101-106. doi:10.1016/j.archger.2007.03.003

121. Stavitsky K, Brickman AM, Scarmeas N, et al. The Progression of Cognition, Psychiatric Symptoms, and Functional Abilities in Dementia With Lewy Bodies and Alzheimer Disease. *Arch Neurol*. 2006;63(10):1450. doi:10.1001/archneur.63.10.1450

122. Bang J, Spina S, Miller BL. Frontotemporal dementia. *The Lancet*. 2015;386(10004):1672-1682.

123. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry*. 1994;57:416-418.

124. Rosen HJ, Gorno–Tempini ML, Goldman WP, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology*. 2002;58(2):198-208. doi:10.1212/WNL.58.2.198

125. Bozeat S. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry*. 2000;69(2):178-186. doi:10.1136/jnnp.69.2.178

126. Ikeda M. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2002;73(4):371-376. doi:10.1136/jnnp.73.4.371

127. Nyatsanza S. A study of stereotypic behaviours in Alzheimer's disease and frontal and temporal variant frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 2003;74(10):1398-1402. doi:10.1136/jnnp.74.10.1398

128. Bathgate D, Snowden JS, Varma A, Blackshaw A, Neary D. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurol Scand*. 2001;103(6):367-378. doi:10.1034/j.1600-0404.2001.2000236.x

129. Snowden JS. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psychiatry*. 2001;70(3):323-332. doi:10.1136/jnnp.70.3.323

130. Chou KR, Kaas MJ, Richie MF. Assaultive behavior in geriatric patients. *J Gerontol Nurs*. 1996;22(11):30-38.

131. Wystanski M. Assaultive behaviour in psychiatrically hospitalized elderly: a response to psychosocial stimulation and changes in pharmacotherapy. *Int J Geriatr Psychiatry*. 2000;15(7):582-585.

132. Nguyen VT, Love AR, Kunik ME. Preventing aggression in persons with dementia. *Geriatrics*. 2008;63(11):21-26.

133. Pulsford D, Duxbury J. Aggressive behaviour by people with dementia in residential care settings: a review. *J Psychiatr Ment Health Nurs*. 2006;13(5):611-618. doi:10.1111/j.1365-2850.2006.00964.x

134. Ticehurst SB, Gale IG, Rosenberg SJ. Homicide and Attempted Homicide by Patients Suffering from Dementia: Two Case Reports. *Aust N Z J Psychiatry*. 1994;28(1):136-140. doi:10.3109/00048679409075855

135. Mendez MF, Shapira JS, Saul RE. The Spectrum of Sociopathy in Dementia. *J Neuropsychiatry Clin Neurosci*. 2011;23(2):132-140. doi:10.1176/jnp.23.2.jnp132

136. Dinniss S. Violent crime in an elderly demented patient. *Int J Geriatr Psychiatry*. 1999;14(10):889-891.

137. Fazel S, Bond M, Gulati G, O'Donnell I. Elderly homicide in Chicago: a research note. *Behav Sci Law*. 2007;25(5):629-639. doi:10.1002/bsl.779

138. Hindley N, Gordon H. The elderly, dementia, aggression and risk assessment. *Int J Geriatr Psychiatry*. 2000;15(3):254-259.

139. GREFEX Study Group, Godefroy O, Martinaud O, et al. The Dysexecutive Syndrome of Alzheimer's Disease: The GREFEX Study. *J Alzheimers Dis*. 2014;42(4):1203-1208. doi:10.3233/JAD-140585

140. Stopford CL, Thompson JC, Neary D, Richardson AMT, Snowden JS. Working memory, attention, and executive function in Alzheimer's disease and frontotemporal dementia. *Cortex J Devoted Study Nerv Syst Behav*. 2012;48(4):429-446. doi:10.1016/j.cortex.2010.12.002

141. Pal A, Biswas A, Pandit A, et al. Study of visuospatial skill in patients with dementia. *Ann Indian Acad Neurol*. 2016;19(1):83-88. doi:10.4103/0972-2327.168636

142. Conejero I, Navucet S, Keller J, Olié E, Courtet P, Gabelle A. A Complex Relationship Between Suicide, Dementia, and Amyloid: A Narrative Review. *Front Neurosci*. 2018;12:371. doi:10.3389/fnins.2018.00371

143. Erlangsen A, Zarit SH, Conwell Y. Hospital-Diagnosed Dementia and Suicide: A Longitudinal Study Using Prospective, Nationwide Register Data. *Am J Geriatr Psychiatry*. 2008;16(3):220-228. doi:10.1097/JGP.0b013e3181602a12

144. Flash Eurobarometer 383: Firearms in the European Union. http://ec.europa.eu/dgs/homeaffairs/what-we-do/policies/organized-crime-and-human-trafficking/trafficking-infirearms/docs/fl383_firearms_report_en.pdf.

145. Aronson L. Don't Ruin My Life — Aging and Driving in the 21st Century. *N Engl J Med*. 2019;380(8):705-707. doi:10.1056/NEJMp1613342

146. Socialstyrelsen. National guidelines for care and care in dementia - Support for management and leadership (socialstyrelsen.se). Published online 2017. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-riktlinjer/2017-12-2.pdf

147. Norton MC, Piercy KW, Rabins PV, et al. Caregiver-Recipient Closeness and Symptom Progression in Alzheimer Disease. The Cache County Dementia Progression Study. *J Gerontol B Psychol Sci Soc Sci*. 2009;64B(5):560-568. doi:10.1093/geronb/gbp052

148. Tschanz JT, Piercy K, Corcoran CD, et al. Caregiver Coping Strategies Predict Cognitive and Functional Decline in Dementia: The Cache County Dementia Progression Study. *Am J Geriatr Psychiatry*. 2013;21(1):57-66. doi:10.1016/j.jagp.2012.10.005

149. Gustafsson M, Sandman PO, Karlsson S, Gustafson Y, Lövheim H. Association between behavioral and psychological symptoms and psychotropic drug use among old people with cognitive impairment living in geriatric care settings. *Int Psychogeriatr*. 2013;25(09):1415-1423. doi:10.1017/S1041610213000859

150. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355(15):1525-1538.

151. Schwertner E, Secnik J, Garcia-Ptacek S, et al. Antipsychotic Treatment Associated With Increased Mortality Risk in Patients With Dementia. A Registry-Based Observational Cohort Study. *J Am Med Dir Assoc*. 2019;20(3):323-329.e2. doi:10.1016/j.jamda.2018.12.019

152. Lopez OL, Becker JT, Chang YF, et al. The long-term effects of conventional and atypical antipsychotics in patients with probable Alzheimer's disease. *Am J Psychiatry*. 2013;170(9):1051-1058.

153. Raivio MM, Laurila JV, Strandberg TE, Tilvis RS, Pitkälä KH. Neither atypical nor conventional antipsychotics increase mortality or hospital admissions among elderly patients with dementia: a two-year prospective study. *Am J Geriatr Psychiatry*. 2007;15(5):416-424.

154. Virginie Gardette, Maryse Lapeyre-Mestre, Nicola Coley, Christelle Cantet, Jean-Louis Montastruc, Bruno Vellas and Sandrine Andrieu. Antipsychotic Use and Mortality Risk in Community-Dwelling Alzheimer's Disease Patients: Evidence for a Role of

Dementia Severity. *Curr Alzheimer Res*. 2012;9(9):1106-1116. doi:10.2174/156720512803569037

155. Tariot PN, Cummings JL, Soto-Martin ME, et al. Trial of Pimavanserin in Dementia-Related Psychosis. *N Engl J Med*. 2021;385(4):309-319. doi:10.1056/NEJMoa2034634

156. Dudas R, Malouf R, McCleery J, Dening T. Antidepressants for treating depression in dementia. Cochrane Dementia and Cognitive Improvement Group, ed. *Cochrane Database Syst Rev*. 2018;2018(8). doi:10.1002/14651858.CD003944.pub2

157. Ruthirakuhan MT, Herrmann N, Abraham EH, Chan S, Lanctôt KL. Pharmacological interventions for apathy in Alzheimer's disease. Cochrane Dementia and Cognitive Improvement Group, ed. *Cochrane Database Syst Rev*. 2018;2018(6). doi:10.1002/14651858.CD012197.pub2

158. Sepehry AA, Sarai M, Hsiung GYR. Pharmacological Therapy for Apathy in Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Can J Neurol Sci J Can Sci Neurol*. 2017;44(3):267-275. doi:10.1017/cjn.2016.426

159. Magierski R, Sobow T, Schwertner E, Religa D. Pharmacotherapy of Behavioral and Psychological Symptoms of Dementia: State of the Art and Future Progress. *Front Pharmacol*. 2020;11:1168. doi:10.3389/fphar.2020.01168

160. McCleery J, Cohen DA, Sharpley AL. Pharmacotherapies for sleep disturbances in dementia. Cochrane Dementia and Cognitive Improvement Group, ed. *Cochrane Database Syst Rev*. Published online November 16, 2016. doi:10.1002/14651858.CD009178.pub3

161. Swedish Medical Products Agency. Läkemedelsbehandling och bemötande vid Beteendemässiga och Psykiska Symptom vid Demenssjukdom—BPSD [Eng. Pharmacological treatment and management of behavioural and psychological symptoms of dementia—BPSD]. Information from the Swedish medical products Agency. Published online 2008.

162. Läkemedelsverket. Läkemedelsbehandling och bemötande vid Beteendemässiga och Psykiska Symtom vid Demenssjukdom – BPSD. Published online 2008. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-riktlinjer/2017-12-2.pdf

163. Kindstedt J, Sjölander M, Lövheim H, Gustafsson M. Psychotropic drug use among older people with major neurocognitive disorder: a cross-sectional study based on Swedish national registries. *Eur J Clin Pharmacol*. Published online November 4, 2021. doi:10.1007/s00228-021-03241-7

164. Lövheim H, Sandman PO, Kallin K, Karlsson S, Gustafson Y. Relationship between antipsychotic drug use and behavioral and psychological symptoms of dementia in old people with cognitive impairment living in geriatric care. *Int Psychogeriatr*. 2006;18(4):713-726. doi:10.1017/S1041610206003930

165. Religa D, Fereshtehnejad SM, Cermakova P, et al. SveDem, the Swedish Dementia Registry. A Tool for Improving the Quality of Diagnostics, Treatment and Care of Dementia Patients in Clinical Practice. Quinn TJ, ed. *PLOS ONE*. 2015;10(2):e0116538. doi:10.1371/journal.pone.0116538

166. Swedish registry for cognitive/dementia disorders (SveDem). Annual report 2020. Published online 2020. https://www.ucr.uu.se/svedem/om-svedem/arsrapporter/svedem-arsrapport-2020/viewdocument/1048

167. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6

168. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*. 2017;89(1):88-100. doi:10.1212/WNL.0000000000004058

169. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry*. 1994;57:416-418.

170. Emre M, Aarsland D, Brown R, Dubois B. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007;22(12):1689-1707.

171. Religa D, Fereshtehnejad SM, Cermakova P, et al. SveDem, the Swedish Dementia Registry – A Tool for Improving the Quality of Diagnostics, Treatment and Care of Dementia Patients in Clinical Practice. Quinn TJ, ed. *PLOS ONE*. 2015;10(2):e0116538. doi:10.1371/journal.pone.0116538

172. Cermakova P, Fereshtehnejad SM, Johnell K, Winblad B, Eriksdotter M, Religa D. Cardiovascular medication burden in dementia disorders: a nationwide study of 19,743 dementia patients in the Swedish Dementia Registry. *Alzheimers Res Ther*. 2014;6(3):34. doi:10.1186/alzrt264

173. Beteendemässiga och psykiska symtom (BPSD) registret. Annual report 2019. https://bpsd.se/wp-content/uploads/2020/11/RSSU008_A%CC%8Arsrapport-2019_TANP_1.4_AVP-byta-till-denna.pdf

174. Bränsvik V, Granvik E, Minthon L, Nordström P, Nägga K. Mortality in patients with behavioural and psychological symptoms of dementia: a registry-based study. *Aging Ment Health*. Published online February 18, 2020:1-9. doi:10.1080/13607863.2020.1727848

175. Wettermark B, Hammar N, MichaelFored C, et al. The new Swedish Prescribed Drug Register—Opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007;16(7):726-735. doi:10.1002/pds.1294

176. Wallerstedt SM, Wettermark B, Hoffmann M. The First Decade with the Swedish Prescribed Drug Register – A Systematic Review of the Output in the Scientific Literature. *Basic Clin Pharmacol Toxicol*. 2016;119(5):464-469. doi:10.1111/bcpt.12613

177. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *Eur J Epidemiol*. 2017;32(9):765-773. doi:10.1007/s10654-017-0316-1

178. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11(1):450. doi:10.1186/1471-2458-11-450

179. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of Neuropsychiatric Symptoms in Dementia and Mild Cognitive Impairment: Results From the Cardiovascular Health Study. *JAMA*. 2002;288(12):1475. doi:10.1001/jama.288.12.1475

180. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

181. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/. Published online 2013.

182. Budescu DV. Dominance analysis: A new approach to the problem of relative importance of predictors in multiple regression. *Psychol Bull*. 1993;114(3):542-551. doi:10.1037/0033-2909.114.3.542

183. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17(4):343-346.

184. Therneau T. A Package for Survival Analysis in S. version 2.38, https://CRAN.R-project.org/package=survival. Published online 2015.

185. Park SH, Goo JM, Jo CH. Receiver operating characteristic (ROC) curve: practical review for radiologists. *Korean J Radiol*. 2004;5(1):11-18. doi:10.3348/kjr.2004.5.1.11

186. Menard S. Six Approaches to Calculating Standardized Logistic Regression Coefficients. *Am Stat*. 2004;58(3):218-223. doi:10.1198/000313004X946

187. Coughlin SS. Ethical issues in epidemiologic research and public health practice. *Emerg Themes Epidemiol*. 2006;3(1):16. doi:10.1186/1742-7622-3-16

188. International guidelines for ethical review of epidemiological studies. *Law Med Health Care Publ Am Soc Law Med*. 1991;19(3-4):247-258.

189. the RADAR-AD Consortium, Muurling M, de Boer C, et al. Remote monitoring technologies in Alzheimer's disease: design of the RADAR-AD study. *Alzheimers Res Ther*. 2021;13(1):89. doi:10.1186/s13195-021-00825-4

190. Zhao QF, Tan L, Wang HF, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord*. 2016;190:264-271. doi:10.1016/j.jad.2015.09.069

191. Kolanowski A, Boltz M, Galik E, et al. Determinants of behavioral and psychological symptoms of dementia: A scoping review of the evidence. *Nurs Outlook*. 2017;65(5):515-529. doi:10.1016/j.outlook.2017.06.006

192. Schnelle JF, MacRae PG, Giacobassi K, MacRae HSH, Simmons SF, Ouslander JG. Exercise with Physically Restrained Nursing Home Residents: Maximizing Benefits of Restraint Reduction. *J Am Geriatr Soc*. 1996;44(5):507-512. doi:10.1111/j.1532-5415.1996.tb01434.x

193. El Haj M, Jardri R, Larøi F, Antoine P. Hallucinations, loneliness, and social isolation in Alzheimer's disease. *Cognit Neuropsychiatry*. 2016;21(1):1-13. doi:10.1080/13546805.2015.1121139

194. Pieper MJC, van Dalen-Kok AH, Francke AL, et al. Interventions targeting pain or behaviour in dementia: a systematic review. *Ageing Res Rev*. 2013;12(4):1042-1055. doi:10.1016/j.arr.2013.05.002

195. Husebo BS, Ballard C, Fritze F, Sandvik RK, Aarsland D. Efficacy of pain treatment on mood syndrome in patients with dementia: a randomized clinical trial: Dep.pain.dem. *Int J Geriatr Psychiatry*. 2014;29(8):828-836. doi:10.1002/gps.4063

196. Habiger TF, Flo E, Achterberg WP, Husebo BS. The Interactive Relationship between Pain, Psychosis, and Agitation in People with Dementia: Results from a Cluster-Randomised Clinical Trial. *Behav Neurol*. 2016;2016:1-8. doi:10.1155/2016/7036415

197. Blytt KM, Bjorvatn B, Husebo B, Flo E. Effects of pain treatment on sleep in nursing home patients with dementia and depression: A multicenter placebo-controlled randomized clinical trial. *Int J Geriatr Psychiatry*. 2018;33(4):663-670. doi:10.1002/gps.4839

198. Erdal A, Flo E, Selbaek G, et al. Associations between pain and depression in nursing home patients at different stages of dementia. *J Affect Disord*. 2017;218:8-14. doi:10.1016/j.jad.2017.04.038

199. Cohen-Mansfield J, Billig N, Lipson S, Rosenthal AS, Pawlson G. Medical Correlates of Agitation in Nursing Home Residents. *Gerontology*. 1990;36(3):150-158. doi:10.1159/000213191

200. Qazi A, Spector A, Orrell M. User, carer and staff perspectives on anxiety in dementia: A qualitative study. *J Affect Disord*. 2010;125(1-3):295-300. doi:10.1016/j.jad.2009.12.015

201. Leonard R, Tinetti ME, Allore HG, Drickamer MA. Potentially Modifiable Resident Characteristics That Are Associated With Physical or Verbal Aggression Among Nursing Home Residents With Dementia. *Arch Intern Med*. 2006;166(12):1295. doi:10.1001/archinte.166.12.1295

202. Blanks JC, Torigoe Y, Hinton DR, Blanks RHI. Retinal pathology in Alzheimer's disease. I. Ganglion cell loss in foveal/parafoveal retina. *Neurobiol Aging*. 1996;17(3):377-384. doi:10.1016/0197-4580(96)00010-3

203. Holth JK, Patel TK, Holtzman DM. Sleep in Alzheimer's Disease–Beyond Amyloid. *Neurobiol Sleep Circadian Rhythms*. 2017;2:4-14. doi:10.1016/j.nbscr.2016.08.002

204. Iseri PK, Altinaş Ö, Tokay T, Yüksel N. Relationship between Cognitive Impairment and Retinal Morphological and Visual Functional Abnormalities in Alzheimer Disease. *J Neuroophthalmol*. 2006;26(1):18-24. doi:10.1097/01.wno.0000204645.56873.26

205. Haasum Y, Fastbom J, Fratiglioni L, Kåreholt I, Johnell K. Pain Treatment in Elderly Persons With and Without Dementia: A Population-Based Study of Institutionalized and Home-Dwelling Elderly. *Drugs Aging*. 2011;28(4):283-293. doi:10.2165/11587040-000000000-00000

206. Mamo SK, Nirmalasari O, Nieman CL, et al. Hearing Care Intervention for Persons with Dementia: A Pilot Study. *Am J Geriatr Psychiatry*. 2017;25(1):91-101. doi:10.1016/j.jagp.2016.08.019

207. Dawes P, Wolski L, Himmelsbach I, Regan J, Leroi I. Interventions for hearing and vision impairment to improve outcomes for people with dementia: a scoping review. *Int Psychogeriatr*. 2019;31(2):203-221. doi:10.1017/S1041610218000728

208. Watt JA, Goodarzi Z, Veroniki AA, et al. Comparative efficacy of interventions for reducing symptoms of depression in people with dementia: systematic review and network meta-analysis. *BMJ*. Published online March 24, 2021:n532. doi:10.1136/bmj.n532

209. Cohen-Mansfield J, Thein K, Marx MS, Dakheel-Ali M, Freedman L. Efficacy of Nonpharmacologic Interventions for Agitation in Advanced Dementia: A Randomized, Placebo-Controlled Trial. *J Clin Psychiatry*. 2012;73(09):1255-1261. doi:10.4088/JCP.12m07918

210. Kinnunen KM, Vikhanova A, Livingston G. The management of sleep disorders in dementia: an update. *Curr Opin Psychiatry*. 2017;30(6):491-497. doi:10.1097/YCO.0000000000000370

211. O'Caoimh R, Mannion H, Sezgin D, O'Donovan MR, Liew A, Molloy DW. Non-pharmacological treatments for sleep disturbance in mild cognitive impairment and dementia: A systematic review and meta-analysis. *Maturitas*. 2019;127:82-94. doi:10.1016/j.maturitas.2019.06.007

212. Kaplan MS, Adamek ME, Rhoades JA. Prevention of elderly suicide. Physicians' assessment of firearm availability. *Am J Prev Med*. 1998;15(1):60-64. doi:10.1016/s0749-3797(98)00019-1

213. Price JH, Kinnison A, Dake JA, Thompson AJ, Price JA. Psychiatrists' Practices and Perceptions Regarding Anticipatory Guidance on Firearms. *Am J Prev Med*. 2007;33(5):370-373. doi:10.1016/j.amepre.2007.07.021

214. Kingswell WJ, Reddan JG, Stedman TJ. What do doctors know, think and do about firearms? *Med J Aust*. 1998;168(3):143-144. doi:10.5694/j.1326-5377.1998.tb126762.x

215. Rothman KJ, Lash TL, VanderWeele TJ, Haneuse S. *Modern Epidemiology*. Fourth edition. Wolters Kluwer; 2021.

216. Ferreira-González I, Marsal JR, Mitjavila F, et al. Patient Registries of Acute Coronary Syndrome: Assessing or Biasing the Clinical Real World Data? *Circ Cardiovasc Qual Outcomes*. 2009;2(6):540-547. doi:10.1161/CIRCOUTCOMES.108.844399

217. Swedish registry for cognitive/dementia disorders (SveDem). Annual report 2019. Published online 2020. https://www.ucr.uu.se/svedem/om-svedem/arsrapporter/svedem-arsrapport-2019/viewdocument/1000.

218. Corrigan PW. How Clinical Diagnosis Might Exacerbate the Stigma of Mental Illness. *Soc Work*. 2007;52(1):31-39. doi:10.1093/sw/52.1.31

219. Robinson L, Clare L, Evans K. Making sense of dementia and adjusting to loss: Psychological reactions to a diagnosis of dementia in couples. *Aging Ment Health*. 2005;9(4):337-347. doi:10.1080/13607860500114555

220. Krueger J. Personal beliefs and cultural stereotypes about racial characteristics. *J Pers Soc Psychol*. 1996;71(3):536-548. doi:10.1037/0022-3514.71.3.536

221. Mischel W, Shoda Y. A cognitive-affective system theory of personality: Reconceptualizing situations, dispositions, dynamics, and invariance in personality structure. *Psychol Rev*. 1995;102(2):246-268. doi:10.1037/0033-295X.102.2.246

222. Merleau-Ponty M, Landes DA. *Phenomenology of Perception*. Routledge; 2012.

223. Bourdieu P. *The Logic of Practice*. Stanford University Press; 1990.

224. Bourdieu P, Nice R. *Outline of a Theory of Practice*.; 2019. Accessed November 23, 2021. https://doi.org/10.1017/CBO9780511812507

225. Kontos PC. Ethnographic reflections on selfhood, embodiment and Alzheimer's disease. *Ageing Soc*. 2004;24(6):829-849. doi:10.1017/S0144686X04002375