Dissertation

zum Erwerb des Doctor of Philosophy (Ph.D.)

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

GERIATRICS PRINCIPLES IN HEALTH CARE OF OLDER ADULTS AND THE USE OF REAL-WORLD DATA IN AGING-RELATED RESEARCH

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Datum der Verteidigung:

_____13.10.2020_____

TABLE OF CONTENTS

ABBREVIATIONS

ADL – Activities of Daily Living

AGS – American Geriatrics Society

FGA – First Generation Antihistamines

HRS – Health and Retirement Study

IADL – Instrumental Activities of Daily Living

ICD9 – International Classification of Diseases, Ninth Revision

NAMCS – National Ambulatory Medical Care Survey

MM – Multiple Myeloma

NDI – National Death Index

PCP – Primary Care Physicians

PRM – Patient Reported Measures

PSM – Propensity Score Matching

RCT – Randomized Controlled Trials

RWD – Real World Data

US – United States

WHO – World Health Organization

1. INTRODUCTION

1.1. Background

The number and proportion of people older than 65 years is growing. It is estimated that 12% of the world population will be 65 years or older in 2030, and by the year 2050, that number will increase to 17%[1]. In the US, the proportion of older adults is even higher, and by 2030, the geriatric population will comprise 20% of the American population[2]. While other special subpopulations, such as pediatrics, are seen as clear special clinical groups, less is invested in terms of research resources and clinical care training to support the care of older adults.

The World Health Organization (WHO) has designated 2020–2030 as a "Decade of Healthy Ageing,"[3] and one of the approaches that WHO has identified to improve the care of older adults is to "develop and ensure access to services that provide older-person-centered and integrated care." This approach is different than the one we usually consider in medical care and healthcare. As WHO states, "Health services are often designed to cure acute conditions or symptoms and tend to manage health issues in disconnected and fragmented ways that lack coordination across care providers, settings and time."[4] While treating each condition separately might work in younger adults, the care that older adults require is different than that required by younger adults. Younger adult patients usually deal with individual health conditions, for which focused care and treatment might be appropriate. Older adults, however, have different medical histories and experiences, which also vary from patient to patient. As people age, they accumulate health conditions, and multimorbidity and chronic conditions become a major part of the health status of older adults. Treating one condition at a time in a patient who suffers from multiple conditions is not only inefficient, but also possibly physiologically impossible. In addition, the treatments themselves are not always appropriate for care in older patients, even if proven to be effective in younger patients. Furthermore, older adults are usually excluded from clinical trials, but

after drug approval, it is assumed that the effect of the drug on an older patient will be the same as that exhibited in younger patients. This assumption is unfounded, since our bodies and organs change as we age: the organs that are responsible for processing medications (the liver and kidneys) function differently in older age, and older patients are therefore exposed to higher risks of adverse effects of medications[5]. Finally, beyond the obvious differences in clinical and physiological conditions, older adults also often have different goals regarding care, and different life circumstances. For example, they might be interested in maintaining independence or a certain level of quality of life at the end of life, and not only in increasing survival time after diagnosis at any cost.

The goal of developing older-person-centered and integrated care must be supported by evidence-based guidelines and standards of care. An important aspect of any research study is obtaining the appropriate data on which to base the results and conclusions. The best evidence usually comes from randomized controlled trials (RCTs), the most common of which are clinical trials. However, older adults are unfortunately often underrepresented in such studies for various reasons, including health, economic burden on the patients and their families, communication issues, and ageism[6,7]. Nevertheless, even if they were regular participants in clinical studies, not every outcome or condition can be studied under such study design. This is especially true in studies in older adults when the exposures of interest might be chronic diseases (e.g. diabetes), long-term health behaviors (e.g. long-term smoking), or mental or cognitive state (e.g. loneliness or dementia). Moreover, the outcomes that are important in older adults might differ from those that are important in the treatment of younger adults (age 18–65). The latter group might be primarily interested in curing a disease or increasing survival time, even if that means enduring severe short-term side effects of therapy. In contrast, older adults might care more about subjective outcomes that are not currently measured in clinical trials. Their outcomes of interest might be more personal, such as managing symptoms and preserving independence and quality of life. In addition, aging is a long-term process, and the outcomes of interest in aging-related research (e.g.

mortality, cognitive and functional decline, chronic symptoms) are usually developed over a number of years, which is not a realistic follow-up time in RCTs. Therefore, these outcomes might be best measured using real-world data (RWDs), such as cohort studies, surveys, longitudinal studies, and administrative data.

In this PhD project, we investigate how taking into consideration unique characteristics of older patients, as well as using appropriate research methods and data to study this group, would allow for better healthcare for this growing part of the population. As part of this PhD project, we performed two studies using RWDs, which examined the role of geriatric principles in care of older adults. In the first study, we used national survey of physicians to examine the use of potentially harmful first generation antihistamines in older adults. In the second study, we examined the patient relevant measures of well-being in older adults diagnosed with multiple myeloma using longitudinal survey and claims data.

The structure of this thesis is as follows. The reminder of Section 1 contains the background on the two topics that the PhD project focuses on – geriatrics principles in health care and RWDs. In subsection 1.2. we starts with describing the geriatric principles of care, and presenting the rationale for using them in clinical care of older adults. Next, in subsection 1.3. we describe what RWDs are, and discuss their potentials and limitations in health care research. Section 2 presents the overall goal of this PhD project, as well as the detailed objectives of each of the two studies that are part of this PhD project. We summarize each study in detail in Section 3, including the methodology, main results, and the studies' contribution to understanding the two topics of the PhD project (geriatric principles in health care and RWDs). The last subsection of Section 3, subsection 3.3., outlines the main conclusions the two PhD studies. Section 4 includes the bibliography of sources used in this PhD project. Finally, section 5 includes the two publications included in this PhD project, as they were published.

1.2. Geriatrics Principles In Health Care

It is becoming increasingly evident in clinical care that a more individualized approach may be more appropriate for the care of older adults. However, the current healthcare systems, most specifically in the US, are not set up to handle the complexities unique to older patients and the individual differences between patients. Clinicians, especially specialists, are often trained to treat the disease that a patient has been diagnosed with, and not the patient and his or her individual circumstances. It has been reported that 32% of the Medicare patients in the US undergo a surgical procedure in the last year of life[8]. While every case is different, and we can make no general statements about the need for or usefulness of those surgeries, it is clear that they were not lifesaving. The surgeries did, however, expose those patients to complications and possible hospital stays[9]. Healthcare decisions should always consider the benefits and risks of the procedures, and those considerations can be different in elderly patients, where the risks might be higher and the benefits lower.

Linos et al. have proposed that clinical care decisions should be made with geriatric principles in mind[2], where decisions are based not only on the characteristics of the diagnosed condition, but also on the characteristics (often aging-related) of the patient. The elements of such a geriatric framework include the following: life expectancy; lag time to benefit; multimorbidity, polypharmacy, and medication adverse effects; and function and cognition. These are explained below.

Life expectancy. The risks and harms of intensive treatments and procedures may outweigh the benefits in patients who have short time to live. One example involves invasive surgeries for skin cancer that can lead to discomfort and complications. While the skin cancer is removed, it likely would not have become a major problem for a patient with a limited life expectancy. Surgery complications, however, do impact the daily life of the patient and might contribute to a decrease in quality of life and other negative outcomes. It has recently been demonstrated and adapted into clinical care that the life expectancy of older adults should play a role when deciding on certain types of cancer screening[10,11] or cancer

treatment[12]. However, it is important not to conflict life expectancy with the chronological age of the patient. While older patients generally have high risks of death, patients' life expectancy at any age can vary significantly depending on their health status. For example, an 80-year-old woman with one or two chronic conditions and no functional impairment has a median life expectancy of 12.6–14.3 years. On the other hand, a 65-year-old man with multiple chronic conditions and difficulty performing some instrumental activities of daily living (e.g. shopping and household chores) has a much shorter life expectancy of 5.0–7.2 years[13]. This indicates that both age and health status should be taken into account when making healthcare decisions.

Lag time to benefit. While all interventions are developed to lead to improved health, not all of them lead to immediate or short-term benefits. This so called "lag time to benefit" has been estimated for many medications and screening procedures[14], and it can vary from an immediate effect to a benefit seen only after several years. For example, Lee et al. showed that it takes approximately 11 years to prevent one death from breast cancer for every 1,000 mammography procedures performed today[15]. This means that in general mammography screenings make sense mostly for women whose life expectancy is longer than 10 years. It is important to balance the lag time to benefit of a specific treatment and the patient's life expectancy when making treatment decisions, as some older patients might not live long enough to experience the benefits of the treatment, but might suffer from its immediate adverse effects and complications[14].

Multimorbidity, polypharmacy, and medication adverse effects. Under similar circumstances, and while being treated for similar conditions, older adults can experience complications that are not common in younger patients. One of the most obvious differences between the groups is that older patients are more likely to experience multimorbidity, since people accumulate health problems as they age. Multimorbidity by itself can be a problem, as the body is less likely to be able to handle additional diseases and treatments. Furthermore, multimorbidity can also lead to polypharmacy, which is

associated with several problems, such as interactions between different medications and overall increased risk of adverse events[16–18]. Another aspect increasing the risk of adverse events in older adults is that physiological differences between younger and older patients. Older patients bodies process the medications differently, and therefore the medications shown safe in younger adults might be risky in older adults[19].

Function and cognition. Functional and cognitive decline are common in older adults. Approximately 20% of older adults report difficulty in performing one or more activities of daily living (bathing, dressing, eating, using the toilet, walking across the room, transferring from bed), and approximately 21% of older adults have cognitive impairment[20]. Some functional and cognitive limitations might affect a patient's ability to receive certain treatments (e.g. by not being able to visit the clinic or not being able to follow instructions). Patients with such functional and cognitive problems often need support from formal or informal caregivers. However, not all older adults have access to such support, and they might thus not be able to adhere to the planned treatment.

The above-mentioned unique characteristics of older patients highlight the importance of physicians being aware of both the most updated guidelines for treatment of older adults and the priorities for older adults. As Linos et al. state[12], "it is possible that some individuals would chose less-invasive treatment if they were given all relevant information. It is also possible that physicians would make different recommendations if they had more guidance (including decision tools or evidence-based guidelines) on this topic."

1.3. Real-World Data

Compiling appropriate data and finding evidence for the relationships between variables are the basis of any research. While the best evidence in medical research usually comes from RCTs, this design is not always possible in practice. In studies of older adults, it might not be possible for the investigator

to set the exposure of interest, which might be chronic diseases (e.g. diabetes), long-term health behaviors (e.g. long-term smoking), or mental or cognitive state (e.g. loneliness or dementia) - all which cannot be altered by the investigator. Moreover, the outcome might only be observed after a long follow-up time, which might not be practical in clinical trial studies. Alternative sources of evidence are observational data, based on RWDs, which includes data sources such as cohort studies, administrative data, and physician surveys. In this PhD project, we differentiate between RWDs that were collected for research purposes (e.g. cohort studies) and RWDs that were not originally intended for use in research (e.g. claims data or administrative data).

We begin with a description of cohort studies. A cohort study involves a group of individuals who are observed, possibly interviewed or completed questionnaires, and followed for a period of time. As opposed to an RCT, where the investigator decides which participants receive the exposure, the participants' exposure in cohort studies is pre-determined (by the participant, environment, or life history) and simply observed by the investigator. The outcome can be either observed as a part of the study or ascertained from links to other data sources (e.g. mortality ascertained from NDI or diagnosis ascertained from claims data or registries).

There are several advantages to using cohort studies in aging-related research. One advantage is that multiple outcomes can be investigated – sometimes outcomes that were not even considered when the study was designed. In addition, the researchers have a high degree of control over what and how data are collected in survey studies, and they can include the exact questions that will address the specific particularities of their research question. Another advantage is that the follow-up time can be long, allowing for the study of long-term outcomes. Finally, in longitudinal studies, it is possible to observe variables before and after the exposure, if the exposure occurs during the study.

Some of the strengths of large cohort studies are also their limitations. For example, the large number of participants and the long follow-up period both make cohort studies expensive. In addition,

as a consequence of the long follow up, the chance of loss to follow up is high, often because of the death of study members before outcomes other than death occur. Another limitation of long-term studies is that healthcare practices, such as diagnostic criteria and treatments, can change during those studies. These changes can affect a researcher's ability to interpret the results.

While cohort studies are designed for research purposes, large amounts of other potentially useful data are also inadvertently being collected every day in a real-world setting. Examples of such data are claims data, healthcare administrative data, and patients' medical chart data, all of which are frequently collected based on convenience; therefore, data collection methods are not consistent with research methods. For example, many health insurance companies capture information on the medical encounters as well as treatments and medications of their customers for payment purposes. However, this data might be problematic for research, since we might only have information on what tests are performed, but not the results thereof. In the same way, we might only have information on procedures performed in a certain hospital, but not those performed on the same patient in other hospitals or outpatient settings. Similarly, we might only have a record of new medications prescribed at a specific doctor's visit and not necessarily all the medications that a patient is taking at the time of the visit.

Despite their limitations, these types of convenience RWDs can still be beneficial in research studies when used carefully and appropriately. While medical records or claims data can be messy because they are administrative data and not research data, and because they are collected usually for reimbursement purposes or for treatment records, such data also have several advantages. Data already exist in charts or computer systems, and access to them can be easier, faster, and cheaper than primary data collection. As a result, we might be able to generate cohorts of large sample sizes almost instantaneously. Furthermore, RWDs reflect real-world patterns of care, not those determined by study protocol. Finally, data mining approaches applied to RWDs can uncover key relationships that are not on clinical radar, thereby generating hypotheses to be studied in further, possibly experimental studies.

Regardless of study design and data type, research studies usually aim to compare two or more groups based on their exposure and to quantify the magnitude of the effect of the exposure on the outcome. Such comparisons are subject to confounding and the consequent biases generated. Confounding is present when subjects' characteristics, both observed and unobserved, are not balanced between two comparison groups[21]. In RCTs, the balance of characteristics is usually achieved in the study design stage, when the groups are randomized before treatment assignment. In contrast, in observational studies, it is impossible to achieve this balance before the group assignment; therefore, it must be considered in the analysis stage.

In the two studies included in this PhD project, we explored the use of matching methods to account for baseline differences in comparison groups. As one of the groups in each study had a small sample size, we had to carefully consider the following issues: matching methods, matching algorithms, and matching ratios[21,22].

In our studies, on the one hand, we explore the potential of the use of RWDs in aging-related research. On the other hand, we investigate and highlight the limitations of such data, and we emphasize the importance of using the appropriate statistical methods in the analysis and accounting for the limitations of the data in the interpretation of the results.

2. OBJECTIVES

The goal of this PhD project is twofold: 1) to examine the role of geriatric principles in care of older adults, 2) to explore the potentials and challenges of using RWDs in epidemiological and health outcomes studies of older adults. The first goal was explored by answering questions about the clinical care of older adults, both from objective (appropriateness of medication prescription and guideline adherence) and subjective (patient experience) perspectives. The second goal was explored by using multiple types of secondary data sources, including a physician survey (the National Ambulatory Medical Care Survey), a longitudinal cohort study (the Health and Requirement Study), and health insurance

claims data (US Medicare data). The results of our studies show how RWDs can be used to shed light on the experience of older adults when being treated for medical conditions. While we identify several limitations of the use of RWDs, we show how studies like this can provide valuable information which can be used to design further research studies on a specific topic.

The specific aims of each of our studies were as follows:

1. To examine medication prescription patterns in older adults – The first study addressed the following questions: Is it possible to assess prescription patterns of physicians based on a national physicians survey? From a clinical perspective, are patient characteristics taken into consideration when prescribing medications to older adults? Are some specialties of physicians more likely to follow the guidelines for appropriate medication prescription for older adults?
2. To examine patient-relevant measures in older adults with multiple myeloma – The second study addressed the following questions: Is it possible to use large-scale longitudinal cohort studies, linked to Medicare data, to identify patients with a specific condition? Can we use cohort studies to describe patient-relevant outcomes and to examine the changes in patients' experiences over time? How do the experiences of patients with a certain condition differ from those of healthy older adults?

3. SUMMARY OF PUBLISHED STUDIES

In this section we describe the two studies published as a part of this PhD project. For each study, we present the rationale for performing the study, the methodology used, and a short summary of the main results. Additionally, we describe how each study explored the two topics discussed in this PhD project – geriatrics principles in care of older adults, and use of RWDs.

3.1. Prescription of First-Generation Antihistamines in Older Adults

The first study included in this thesis is titled, "A Multi-Year Cross-Sectional Study of US National Prescribing Patterns of First-Generation Sedating Antihistamines in Older Adults with Skin Disease." It was accepted for publication in the British Journal of Dermatology on April 25th, 2019.

Rationale: The clinical background for this study concerns the safe prescribing of first-generation antihistamines (FGAs) to older patients. Due to several known side effects in older adults (e.g. cognitive impairment, falls ,confusion, and constipation[23–27]) the American Geriatrics Society (AGS) categorizes FGAs as potentially inappropriate for older patients[19]. In this study we examined the prescription rate of FGAs to older patients, and compared that rate among several subgroups (i.e., older vs. younger patients, different diagnoses, dermatologists vs. primary care physicians).

Methods: We used data from the US National Ambulatory Medical Care Survey (NAMCS), between years 2006 and 2015, and we included in the study the visits of adult patients to dermatology offices and primary care physician (PCP) offices. The main outcome was prescription of any first generation antihistamine, which was reported by the treating physician at the time of the visit. Other main variables were: physician specialty, patient's age and gender, diagnoses and other prescriptions at the time of the visit, and reason for visit. We compared the patients across different subgroups using χ^2 tests. We determined if any patient and physician characteristics were independently associated with FGA prescription using multivariate logistic regression. Finally, we assessed the differences between dermatology and PCP visits using propensity score matching (PSM), to account for differences in patient characteristics between those two specialties.

Main Results: Our study showed that dermatologists prescribed FGAs in 1.5% of visits by adults over 65 years, which is similar to the prescription rate of younger patients (1.2%, *p*-value=0.19). We observed some differences between older adults with and without FGA prescriptions: those with FGA

prescriptions were more likely to have a diagnosis of dermatitis or pruritus, report an itch as the reason for their visit, have a chronic problem, and have six or more prescriptions at the visit. However, we did not find any association between FGA prescription and age, gender, or multimorbidity.

The prescription rate of FGAs among older patients in PCP offices significantly higher than the rate in dermatology offices (4.5% vs. 1.5%, *p*-value < 0.001). Propensity score matching which included patient and visit characteristics revealed that even in the matched samples, the FGA prescriptions at dermatology visits were still lower than the rate at PCP visits (3.9% dermatology visits vs. 7.4% PCP visits, *p*-value = 0.02).

Relevance to Geriatrics Principles: FGA prescription rates are similar regardless of age, gender, and multimorbidity, suggesting that many physicians do not follow geriatric principles, and are therefore potentially putting older and sicker patients at risk of adverse events, without evidence that those medications provide the desired therapeutic benefit to those patients.[28] Our findings also show that dermatologists were less likely than primary care doctors to prescribe an FGA to patients with the same skin conditions or in similar clinical circumstances.

Use of RWDs: Through the nationally representative cross-sectional survey of physicians, we had information on basic patient demographics, and diagnoses and medications for each office visit reported. While this kind of data gives a real-life picture of how physicians prescribe medications it also has several limitations: (1) the maximum number of reported prescriptions increased from eight in 2006 to 30 by 2015, which might have changed the probability of recording FGAs over time. (2) physicians are not required to report a diagnosis code for the prescriptions, so we cannot assess the reason for prescribing FGA; (3) physicians are asked to record only the medications they prescribe at a specific visit, and this can lead to exclusion of FGA prescription prescribed on another visit that are still being taken by the patient; (4) similarly, we cannot assess cumulative anticholinergic burden[29] since we only have prescriptions from a specific visit.

Summary: The results of our study indicate that physicians overall do not follow the guidelines of the AGS for FGA prescriptions to older adults. Our study also demonstrates that different clinical specialists might be following different prescription patterns. Therefore, it might be possible to improve the care of older adults with dermatological conditions by encouraging a collaboration between dermatologists, geriatricians, and PCPs. Dermatologists might be more aware of proper treatments for skin conditions; geriatricians might be more aware of risks unique to older adults; and PCPs are most familiar with their patients' overall health status and medical history. All three of those viewpoints are essential for the optimal care of older adults.

Candidate contribution: The candidate (IC) was developed the concept of the study together with the senior author (Dr. Eleni Linos), and was responsible for designing and performing the analysis of the data and interpreting the results. The candidate also wrote the full manuscript.

3.2. Patient-Reported Measures in Multiple Myeloma Patients

The second study included in this thesis is titled, "Patient-Reported Measures of Well-Being in Older Multiple Myeloma Patients: Use of Secondary Data Source." It was accepted for publication in Aging Clinical and Experimental Research on December 23rd, 2019.

Rationale: Multiple myeloma (MM) is a rare disease that disproportionately affects older patients[30]. Due to its low prevalence in the population, recruitment of large number of multiple myeloma patients into research studies can be difficult. Here we aim to show that it is possible to create study cohorts of multiple myeloma patients using secondary data. The clinical side of the study focuses on the patient experience of the older multiple myeloma patients. We know that recent pharmaceutical developments lead to new treatments that increase the survival time in multiple myeloma patients[31]. However, it is not clear how the quality of life of older adults is affected by these treatments.

Understanding those effects is important, since older patients are more likely to suffer from treatment-related adverse events than younger patients, but are at the same time more concerned with symptom management, the maintaining of independence, and quality of life[32]. In this study we examine the changes in patients' well-being, and how these changes compare to changes attributed solely to aging of healthy older adults.

Methods: In this study we identified older MM patients using the Health and Retirement Study (HRS) and Medicare claims. The measures evaluated in this study included activities of daily living (ADL) and instrumental activities of daily living (IADL) impairment, difficulty with walking and climbing stairs, vision and hearing impairment, significant pain, self-rated health, and depression. Those measures describe several aspects of well-being of older patients, and are included in the geriatric assessment[33,34]. We used McNemar's test to compare the frequency of patient-reported measures (PRM) from before and after multiple myeloma diagnosis. Additionally, we used propensity score matching to compare change in PRMs between multiple myeloma patients and healthy older adults with similar baseline characteristics over the same time period.

Main Results: We had access to Medicare claims of 26,044 HRS participants, and we were able to identify 92 patients with multiple myeloma in this sample. Our study showed an increase in impairments of PRMs after the multiple myeloma diagnosis, including increases in frequency of ADL difficulty, difficulty walking several blocks, and difficulty climbing one flight of stairs. Additionally, more patients reported experiencing hearing impairment, depression symptoms, and reporting poor or fair self-rated health after multiple myeloma diagnosis.

Comparable HRS participants without MM diagnosis also reported increase in most impairments of PRM over the same period of time, but the increase was smaller than the one experienced by MM patients. For example, while 40% of the MM patients experienced increase in difficulty performing ADLs, 27% of the HRS participants without MM diagnosis experienced it (*p*-value = 0.04). Similarly, the

frequency of participants reporting depression symptoms is more than double among MM patients compared to HRS participants without the diagnosis (11% vs. 29%, $p = 0.003$).

Relevance to Geriatrics Principles: Our study showed that measures that are important to older patients worsen after multiple myeloma. However, the patient reported measures that we examined in our study are not usually considered priorities in treatment of older persons with cancer, and they are rarely considered as outcomes in clinical trials of cancer treatments. We have also observed high mortality rate in our sample of older adults (20% one-year mortality). This high mortality rate and the reported decline in well-being suggest that supportive geriatric and palliative care should be a part of care of older patients with multiple myeloma.

Use of RWDs: Our study demonstrated the following advantages of using longitudinal studies in research: (1) in studies with long study period, we can observe over time enough cases of even rare diseases; (2) because of the longitudinal nature of HRS, each participant is interviewed every two years. This means all measures are potentially observed before and after the diagnosis; (3) we have the same measures of well-being for a large sample of participants without multiple myeloma diagnosis. This means that we can use those healthy participants to compare changes in the well-being between healthy participants and patients with multiple myeloma diagnosis.

Our study also demonstrates several limitations: (1) multiple myeloma was identified from Medicare claims using ICD9 codes, but Medicare data does not include any test results that could confirm these diagnoses; (2) We cannot explain if the changes in the well-being are due to the disease itself or specific treatments, since in our Medicare files we do not have information on treatments; (3) HRS interviews are conducted every two years, and are of course independently scheduled from multiple myeloma diagnosis. This means that the time between an interview and the diagnosis can

range from 0 days to two years, during which time the health status and the well-being of patients can change.

Summary: We showed that it is possible to use secondary data to identify patients with rare diseases and create feasible study samples. While this and similar studies might be limited by some aspects of data collection, they still provide valuable exploratory and hypotheses-generating information. As showed by the results of this study, well-being of older patients worsens after MM diagnosis, and the decline and the mortality rate in this group are larger than the decline and mortality rate that healthy older adults experience as a normal part of aging. This indicates that multiple myeloma treatments of older patients should include not only the treatment of the disease itself, but also supportive geriatric and palliative care.

Candidate contribution: The candidate (IC) developed the idea and the concept for the study, and she was responsible for performing the analysis of the data and interpreting the results. The candidate also wrote the full manuscript and prepared the poster for the presentation at the DAGStat conference in Munich in March 2019.

3.3. Conclusions

We performed two studies leveraging the use of RWDs in epidemiological and health outcomes research in the aging population. The two overall goals of the studies were to examine the use of the geriatric principles in clinical care of older adults and to assess the potentials of using RWDs in aging-related research. Our studies have demonstrated that when analyzed appropriately and interpreted carefully, RWDs can be used to describe basic patterns of care and patient experience. While the use of RWDs unavoidably leads to some limitations in our studies, the results are nevertheless valuable in understanding the care and experience of older patients. The information obtained in these studies can

be used to generate hypotheses and design further studies. For example, our multiple myeloma study found that patient-reported measures are significantly affected after the diagnosis and those measures should thus be included in clinical trials.

Regardless of the type of data used, our studies also highlight the importance of considering the geriatrics principles in clinical care of older adults. Physicians should balance the benefits and harms for an individual patient, as well as patient's personal preferences. Physicians should consequently not follow one-size-fits-all guidelines. The guidelines for and the practice of clinical care for older adults should consider each patient's unique characteristics, such as general health status, polypharmacy, cognition, and patient and family preferences.

4. BIBLIOGRAPHY

1. The ISPOR Student Network. By the Numbers: Aging of the Global Population. *Value & Outcomes Spotlight*. 2019:22. https://www.ispor.org/docs/default-source/publications/value-outcomes-spotlight/september-october-2019/feature---by-the-numbers.pdf?sfvrsn=b05613d4_0.
2. Linos E, Chren M, Covinsky K. Geriatric dermatology—a framework for caring for older patients with skin disease. *JAMA Dermatology*. 2018;154(7):757-758. http://dx.doi.org/10.1001/jamadermatol.2018.0286.
3. World Health Organization. Decade of Healthy Ageing. https://www.who.int/ageing/decade-of-healthy-ageing. Accessed January 24, 2020.
4. World Health Organization. Ageing and life-course. https://www.who.int/ageing/health-systems/en/. Accessed January 24, 2020.
5. Aronson L. *Elderhood*. New York, NY: Bloomsbury Publishing; 2019.
6. Herrera AP, Snipes SA, King DW, Torres-Vigil I, Goldberg DS, Wenberg AD. Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change. *Am J Public Health*. 2010. doi:10.2105/AJPH.2009.162982
7. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: Race-, sex-, and age-based disparities. *J Am Med Assoc*. 2004. doi:10.1001/jama.291.22.2720
8. Kwok AC, Semel ME, Lipsitz SR, et al. The intensity and variation of surgical care at the end of life: A retrospective cohort study. *Lancet*. 2011. doi:10.1016/S0140-6736(11)61268-3
9. Linos E, Wehner MR, Frosch DL, Walter L, Chren MM. Patient-reported problems after office procedures. *JAMA Intern Med*. 2013. doi:10.1001/jamainternmed.2013.1040
10. Walter LC, Covinsky KE. Cancer Screening in Elderly Patients. *JAMA*. 2001. doi:10.1001/jama.285.21.2750
11. Walter LC, Bertenthal D, Lindquist K, Konety BR. PSA screening among elderly men with limited life expectancies. *J Am Med Assoc*. 2006. doi:10.1001/jama.296.19.2336
12. Linos E, Chren M-M, Stijacic Cenzer I, Covinsky KE. Skin Cancer in U.S. Elderly Adults: Does Life Expectancy Play a Role in Treatment Decisions? *J Am Geriatr Soc*. 2016. doi:10.1111/jgs.14202
13. Lee S, Smith A, Widera E, Yourman L, Schonberg M, Ahalt C. ePrognosis - Estimating Prognosis for Elders. https://eprognosis.ucsf.edu/index.php. Accessed January 24, 2020.
14. Lee SJ, Leipzig RM, Walter LC. Incorporating lag time to benefit into prevention decisions for older adults. *JAMA - J Am Med Assoc*. 2013. doi:10.1001/jama.2013.282612
15. Lee SJ, Boscardin WJ, Stijacic-Cenzer I, Conell-Price J, Sarah O, Walter LC. Time lag to benefit after screening for breast and colorectal cancer: Meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. *BMJ*. 2013. doi:10.1136/bmj.e8441
16. Patterson SM, Cadogan CA, Kerse N, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev*. 2014. doi:10.1002/14651858.CD008165.pub3
17. Steinman MA, Handler SM, Gurwitz JH, Schiff GD, Covinsky KE. Beyond the prescription: Medication monitoring and adverse drug events in older adults. *J Am Geriatr Soc*. 2011. doi:10.1111/j.1532-5415.2011.03500.x
18. Steinman MA. Polypharmacy - Time to get beyond numbers. *JAMA Intern Med*. 2016. doi:10.1001/jamainternmed.2015.8597
19. Samuel MJ. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015. doi:10.1111/jgs.13702
20. Health and Retirement Study. http://hrsonline.isr.umich.edu/. Accessed March 15, 2019.
21. Austin PC. An introduction to propensity score methods for reducing the effects of confounding

in observational studies. *Multivariate Behav Res*. 2011. doi:10.1080/00273171.2011.568786
22. Stuart EA. Matching Methods for Causal Inference: A Review and a Look Forward. *Stat Sci*. 2010;25(1):1-21. doi:10.1214/09-STS313
23. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging*. 2009. doi:10.2147/CIA.S5358
24. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: A prospective cohort study. *JAMA Intern Med*. 2015. doi:10.1001/jamainternmed.2014.7663
25. Doraiswamy PM, Husain MM. Anticholinergic drugs and elderly people: a no brainer? *Lancet Neurol*. 2006. doi:10.1016/S1474-4422(06)70421-5
26. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: Longitudinal cohort study. *Br Med J*. 2006. doi:10.1136/bmj.38740.439664.DE
27. Risacher SL, McDonald BC, Tallman EF, et al. Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. *JAMA Neurol*. 2016. doi:10.1001/jamaneurol.2016.0580
28. He A, Feldman SR, Fleischer AB. Trends in Atopic Dermatitis Management: Comparison of 1990-1997 to 2003-2012. *J Drugs Dermatol*. 2018.
29. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: A systematic review. *BMC Geriatr*. 2015. doi:10.1186/s12877-015-0029-9
30. Noone A.M., Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis D.R., Chen H.S., Feuer E.J., Cronin K.A. (eds). *SEER Cancer Statistics Review*.; 2017.
31. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: Changes in early mortality and outcomes in older patients. *Leukemia*. 2014. doi:10.1038/leu.2013.313
32. Wildes TM, Rosko A, Tuchman SA. Multiple myeloma in the older adult: Better prospects, more challenges. *J Clin Oncol*. 2014. doi:10.1200/JCO.2014.55.1028
33. Elsawy B, Higgins KE. The geriatric assessment. *Am Fam Physician*. 2011.
34. Mariano J, Min LC. Chaper 4 - Assessment. In: *Management of Cancer in the Older Patient*. ; 2012:39-50.

5. PUBLICATIONS

5.1. A Multi-Year Cross-Sectional Study of US National Prescribing Patterns of First-Generation Sedating Antihistamines in Older Adults with Skin Disease.

GENERAL DERMATOLOGY

BJD
British Journal of Dermatology

A multiyear cross-sectional study of U.S. national prescribing patterns of first-generation sedating antihistamines in older adults with skin disease

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Accepted for publication
23 April 2019

Funding sources
E.L. is supported by the National Institute on Aging (K76AG054631). M.W. is supported by a National Institute of Arthritis and Musculoskeletal and Skin Diseases/National Institute of Health Dermatology Research Training Grant (no. T32 AR7465; principal investigator, Sarah E. Millar). The funding is by NIAMS (National Institute of Arthritis and Musculoskeletal and Skin Diseases), and the grant number is **K24 AR075060**.

Conflicts of interest
None to declare.

DOI 10.1111/bjd.18042

Summary

Background First-generation antihistamines (FGAs) are classified as 'potentially inappropriate' for use in older patients (patients aged ≥ 65 years). However, the prevalence of and factors associated with FGA prescription have not been studied.
Objectives To examine FGA prescription rates for older patients who visited dermatology offices, and compare them to those for younger patients (patients aged 18–65 years) who visited dermatology offices and those for older patients who visited primary-care physicians (PCPs).
Methods This was a multiyear cross-sectional observational study using data from the U.S. National Ambulatory Medical Care Survey (2006–2015). Visits by patients aged 18 years or older were included in the study; the data comprised 15 243 dermatology office visits and 66 036 PCP office visits. The main outcome was FGA prescription. Other variables included physician specialty (dermatologist or PCP), patient's age, diagnosis of dermatological conditions and reason for visit.
Results For dermatology visits, the overall FGA prescription rate for older patients was similar to that for younger patients (1·5% vs. 1·2%; P = 0·19), even when the diagnosis was dermatitis or pruritus (3·7% vs. 4·8%; P = 0·21) or when itch was a complaint (7·6% vs. 6·7%; P = 0·64). However, the rate of FGA prescription for dermatology visits was lower than that for PCP visits, in analyses matched for patient and visit characteristics (3·9% vs. 7·4%; P = 0·02).
Conclusions Our findings suggest that FGAs are overprescribed to older patients but that dermatologists are less likely to prescribe FGAs than PCPs.

What's already known about this topic?

- First-generation antihistamines (FGAs) have been shown to pose substantial risks to older adults, including cognitive impairment, falls, confusion, dry mouth and constipation.
- Therefore, FGAs have been classified as 'potentially inappropriate' for use in older patients by the American Geriatrics Society.
- It has also been shown that dermatologists do not always take patient characteristics (e.g. age or life expectancy) into account when deciding on a treatment, instead following a 'one-size-fits-all' approach.

What does this study add?

- FGAs are often prescribed during dermatology visits, and prescription rates do not differ between older and younger patients.
- There were no significant differences in prescription rates when comparing younger and older adults with the same diagnosis or symptom (e.g. dermatitis, pruritus or itch).
- FGAs are prescribed at higher rates in primary-care offices than in dermatology offices.

By 2030, one in five Americans will be over the age of 65 years, with the fastest-growing segment of the U.S. population – those over the age of 85 years – expected to double from 4·7 million in 2003 to 9·6 million in 2030.[1] As the number of older adults continues to increase, there is an urgent need to incorporate the principles of geriatrics into the clinical practice of dermatology.[1] One such principle is the safe prescribing of medications, which has been identified by the American Geriatrics Society (AGS) as a priority.

First-generation antihistamines (FGAs) are used to treat skin diseases, including chronic pruritus. This is particularly relevant, as the symptom of chronic pruritus or itch is especially common among older adults and accounts for almost 7 million physician visits each year.[2] However, the vast majority of itch experienced by older adults is not histamine mediated,[3] making the benefit of these prescriptions questionable. In addition, the fact that FGAs are synthesized from chemical stems similar to those used for the synthesis of anticholinergic agents leads to receptor nonspecificity and consequent anticholinergic side-effects. It has been shown that anticholinergic medications pose substantial risks to older adults and have been linked to cognitive impairment, falls and side-effects such as confusion, dry mouth and constipation.[4–9] Moreover, FGAs are able to cross the blood–brain barrier and so can affect the sleep–wake cycle, memory and concentration.[10] Thus, FGAs have been classified as 'potentially inappropriate' for use in older adults: the AGS recommends providers 'avoid' them and lists the strength of that recommendation as 'strong', due to their significant anticholinergic effects.[4]

In this study, we examine FGA prescriptions in older patients with skin disease, and compare the prescription rates with those of younger patients. We hypothesized that certain subgroups, such as the oldest patients, would receive fewer FGAs, given the increased risks of adverse effects in older patients. Additionally, we examined the differences in prescription patterns between dermatologists and primary-care physicians (PCPs). We hypothesized that dermatologists are more aware of the risks of antihistamines, and their lack of efficacy in most forms of chronic pruritus, and would therefore be less likely to prescribe them.

Patients and methods

Data source

The National Ambulatory Medical Care Survey (NAMCS) is a national survey designed to collect information about the use of ambulatory medical care services in the U.S.A.[11] Information is collected from the physicians on a sample of patient visits to nonfederally employed, office-based physicians. Each participating physician is assigned to a 1-week reporting period, during which, information on visits is abstracted using the Patient Record form.[12] Data obtained during the visit include patient demographics, the patient's reason for the visit (including symptoms), the physician's diagnoses, services ordered or provided and treatments (including medications). Additionally, basic information about the physician and his or her practice is collected.

We analysed the NAMCS dataset for the years 2006–2015. During this time, between 1300 and 3800 physicians participated every year, with an average response rate of 50·2%.[13] We limited our analyses to visits by patients aged 18 years or older, because dermatological symptoms in younger patients might be caused by different mechanisms and can be treated differently. Additionally, we only considered visits in two subspecialties: dermatology and primary care. This resulted in a sample of 81 279 visits: 15 243 visits to a dermatology office, and 66 036 visits to a PCP office.

Measures

For each visit, we identified whether the visit resulted in a prescription (new or continued) of FGAs, as recorded on the Patient Form in response to the question 'Were any prescriptions or non-prescription drugs ORDERED or PROVIDED (by any route of administration) at this visit?'. The number of possible medications reported ranged from eight in 2006 to 30 in 2015. The list of medications used to identify FGAs is reported in Table 1. We also collected information on multimorbidity, which was defined as the presence of two or more of the following conditions: arthritis, cancer, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, depression, diabetes and hypertension. The

Table 1 List of first-generation antihistamines included in the study

Brompheniramine
Carbinoxamine
Chlorcyclizine
Chlorpheniramine
Clemastine
Cyproheptadine
Dexbrompheniramine
Dexchlorpheniramine
Dimenhydrinate
Diphenhydramine (oral)
Doxylamine
Hydroxyzine
Meclizine
Methapyrilene
Phenindamine
Pheniramine
Phenyltoloxamine
Promethazine
Pyrilamine
Tripelennamine
Triprolidine

presence of any one of these conditions was assessed with the response to the question 'Regardless of the diagnoses previously entered, does the patient now have –', which was accompanied on the form by a list of potential conditions. Polypharmacy was defined as the prescription of six or more medications at the visit.[14] Diagnoses related to the visit were recorded using the response to the question 'As specifically as possible, list diagnoses related to this visit including chronic conditions'. A diagnosis of dermatitis was identified by the use of the International Classification of Diseases 9th Revision (ICD9) codes 691.xx, 692.xx, 693.xx and 708·0, and a diagnosis of pruritus (itch) was identified by the use of the ICD9 code 698.xx. The symptom of itch was identified from the response to the question 'List the first 5 reasons for visit (i.e. symptoms, problems, issues, concerns of the patient) in the order in which they appear. Start with the chief complaint and then move to the patient history for additional reasons'. Visits for which itch was listed as any one of the five reasons were included in the analysis. In addition, for each visit, we determined whether the payment had been covered by private insurance or one of the following nonprivate sources: Medicare; Medicaid, Children's Health Insurance Program or some other state-based programme; self-pay; or some other source.

Analysis

Firstly, we examined the characteristics of older patients (defined as patients ≥ 65 years old) who visited a dermatologist, and compared the number of patients who received FGA prescriptions at their visits with that of those who did not. The goal was to identify possible factors associated with FGA prescription in older adults. Factors considered were age (65–74 years vs. ≥ 75 years), sex, race (white vs. nonwhite), insurance type (private vs. nonprivate), reason for the office visit (chronic vs. nonchronic problem), the presence of two or more chronic conditions, polypharmacy, a diagnosis of dermatitis or pruritus, and listing itch as a symptom.[15] Following the univariate analyses, we performed multivariate logistic regression to assess whether any of the risk factors identified in the unadjusted analyses remained associated in the adjusted analysis. The regression model included all the variables described above. Reports missing values for insurance type ($n = 222$) or the reasons for the visit ($n = 109$) were excluded from the multivariate analysis.

Next, we compared the FGA prescription rates for younger dermatology patients (those aged 18–65 years) and older dermatology patients, overall and in two subgroups: those with a diagnosis of dermatitis or pruritus, and those with itch as a symptom. The differences were assessed using the χ-test.

Finally, we compared the rates at which FGAs were prescribed to older patients at PCP office visits with the rates at which FGAs were prescribed to older patients at dermatology office visits. Firstly, we examined the prescription rates for visits by older patients to either a PCP office or a dermatology office, comparing two subgroups of patients: patients with a diagnosis of dermatitis or pruritus, and patients who presented with itch as a symptom. Next, because PCPs and dermatologists see patients with different medical conditions, we limited the sample of PCP office visits to only those visits with at least one of the 50 most common dermatological diagnoses.[16] In order to account further for any possible differences between demographic or health factors for patients visiting a dermatology office and those visiting a PCP office, we matched patients with common dermatological diagnoses, using propensity score matching.[17] In the matching process, we accounted for the following variables: age (65–74 years vs. ≥ 75 years), sex, race (white vs. nonwhite), type of insurance (private vs. nonprivate), reason for the office visit (chronic vs. nonchronic problem), multicomorbidity, polypharmacy and whether the visit took place before or after 2012 (the year the Beers criteria for potentially inappropriate medication use in older adults were first published). Propensity score matching identified pairs of patients, one of whom had visited a dermatology office and one who had visited a PCP office, who had similar probabilities of being dermatology patients, given the variables above. The FGA prescription rates in the two matched groups were then compared using McNemar's test.

We report the unweighted raw number of surveys completed, and the weighted percentages those surveys represent after adjusting for survey weights and design factors. Statistical analyses were performed using SAS 9·4 (SAS Institute Inc., Cary, NC, U.S.A.) and Stata/MP 14 (StataCorp, College Station, TX, U.S.A.).[18,19]

Results

From the NAMCS dataset, we identified 15 243 visits to dermatologists. Of these, 5967 (39%) were by older patients (Table 2). Of these, 50% were women, the majority were

Table 2 Characteristics of dermatology patients aged 65 years or over, and adjusted odds ratios for first-generation antihistamine prescription

Characteristics	Total, n (%)	No FGA prescription, n (%)	FGA prescription, n (%)	Unadjusted P-value	Adjusted OR (confidence interval)	Adjusted P-value
Unweighted n	5967	5871	96	–	–	–
Weighted n	121 269 336	119 457 990	181 1346	–	–	–
Age (years)						
65–75	3010 (50)	2959 (50)	51 (53)	0·66	1	0·28
≥ 75	2957 (50)	2912 (50)	45 (47)		0·7 (0·4–1·3)	
Sex						
Female	2937 (50)	2877 (50)	60 (63)	0·07	1	0·22
Male	3030 (50)	2994 (50)	36 (37)		0·7 (0·3–1·3)	
Race and ethnicity						
Nonwhite	446 (7)	431 (7)	15 (13)	0·04	1	0·25
White	5521 (93)	5440 (93)	81 (87)		0·6 (0·3–1·4)	
Insurance type						
Nonprivate	4710 (82)	4634 (82)	76 (89)	0·10	1	0·24
Private	1035 (18)	1017 (18)	18 (11)		0·7 (0·3–1·3)	
Reason for visit						
Nonchronic problem	3334 (57)	3284 (58)	50 (44)	0·05	1	0·06
Chronic problem	2524 (43)	2479 (42)	45 (56)		1·8 (1–3·2)	
Number of comorbid conditions						
< 2	4521 (77)	4453 (77)	68 (79)	0·67	1	0·14
≥ 2	1446 (23)	1418 (23)	28 (21)		0·5 (0·2–1·3)	
Number of medications						
< 6	5022 (87)	4973 (88)	49 (60)	< 0·001	1	< 0·001
≥ 6	945 (13)	898 (12)	47 (40)		4·7 (2·2–10·1)	
Diagnosis of dermatitis and/or pruritus[a]						
No	5118 (86)	5058 (87)	60 (66)	< 0·001	1	0·01
Yes	849 (14)	813 (13)	36 (34)		2·2 (1·2–3·9)	
Itch symptom						
No	5710 (95)	5633 (95)	77 (73)	< 0·001	1	< 0·001
Yes	257 (5)	238 (5)	19 (27)		4·7 (2·1–10·9)	

FGA, first-generation antihistamine. [a]International Classification of Diseases 9th Revision (ICD9) codes for dermatitis: 691.xx, 692.xx, 693.xx and 708·0; ICD9 code for pruritus (itch): 698.xx.

white (93%) and 82% had nonprivate insurance. The most common diagnoses coded by physicians were actinic keratosis; malignant neoplasm of skin; other seborrheic keratosis; contact dermatitis or other eczema; and personal history of malignant neoplasm of skin. Overall, 14% of these visits resulted in a diagnosis of pruritus or dermatitis. The most common reasons for these visits were skin lesions, discoloration or abnormal pigmentation, skin cancer and skin rash. Itch was reported by patients as a reason for the visit in 5% of visits. FGAs were prescribed in 1·5% of visits to dermatologists by older patients.

Older dermatology patients with FGA prescriptions were more likely to have been diagnosed with dermatitis or pruritus (34% vs. 13%, $P < 0·001$), more likely to have reported itch as a reason for the visit (27% vs. 5%, $P < 0·001$), less likely to be white (87% vs. 93%, $P = 0·04$), more likely to have a chronic problem (56% vs. 42%, $P = 0·05$) and more likely to have six or more prescriptions at the visit (40% vs. 12%, $P < 0·001$), compared with older dermatology patients without FGA prescriptions. Age, sex, insurance type and multicomorbidity were not associated with FGA prescription in older patients during dermatology visits (Table 2). In analyses adjusted for demographics, health and visit characteristics, we found that polypharmacy [adjusted odds ratio (AOR) 4·7, 95% confidence interval (95% CI) 2·2–10·1], a diagnosis of dermatitis or pruritus (AOR 2·2, 95% CI 1·2–3·9) and itch being listed as a reason for the visit (AOR 4·7, 95% CI 2·1–10·9) remained associated with FGA prescription (Table 2).

For the 15 243 visits to dermatologists, FGA prescription rates for younger patients were similar to those for older patients; specifically, there was no significant difference in the overall FGA prescription rates (1·2% for younger patients vs. 1·5% for older patients; $P = 0·19$). Furthermore, there were no significant differences in FGA prescription rates between visits with a diagnosis of dermatitis or pruritus (4·8% for younger patients vs. 3·7% for older patients; $P = 0·21$) or visits during which itch was reported as a reason for the visit (6·7% for younger patients vs. 7·6% for older patients; $P = 0·64$; Table 3).

Of the 66 036 visits to PCPs, 16 995 (25·7%) were by older patients. The overall FGA prescription rate for older patients for visits to a PCP office was 4·5%. Patients with a

Table 3 First-generation antihistamine (FGA) prescription rates for younger dermatology patients (patients aged 18–65 years) vs. those for older dermatology patients (patients aged ≥ 65 years), according to diagnosis subgroup

Characteristics	FGA prescription rates for younger patients, n/N (%)	P-value	FGA prescription rates for older patients, n/N (%)	P-value	P-value for younger vs. older patients
Overall	135/9276 (1·2)	–	96/5967 (1·5)	–	0·19
Diagnosis of dermatitis and/or pruritus					
No	66/7925 (0·6)	< 0·001	60/5118 (1·1)	< 0·001	< 0·01
Yes	69/1351 (4·8)		36/849 (3·7)		0·21
Itch symptom					
No	112/8960 (1·0)	< 0·001	77/5710 (1·2)	< 0·001	0·48
Yes	23/316 (6·7)		19/257 (7·6)		0·64

Table 4 First-generation antihistamine (FGA) prescriptions for patients aged 65 and over for dermatology office visits vs. those for primary-care physician (PCP) office visits

Characteristics	FGA prescription rates for dermatology office visits, n/N (%)	P-value	FGA prescription rates for PCP office visits, n/N (%)	P-value	P-value for dermatology vs. PCP visits
Overall	96/5967 (1·5)	–	791/16995 (4·5)	–	< 0·001
Diagnosis of dermatitis and/or pruritus					
No	60/5118 (1·1)	< 0·001	757/16777 (4·3)	< 0·001	< 0·001
Yes	36/849 (3·7)		34/218 (14·3)		< 0·001
Itch symptom					
No	77/5710 (1·2)	< 0·001	778/16913 (4·4)	< 0·001	< 0·001
Yes	19/257 (7·6)		13/82 (14·7)		0·02

diagnosis of dermatitis or pruritus were more likely to be prescribed FGAs in PCP offices than were those with other diagnoses (14·3% vs. 4·3%, P < 0·001). Similarly, patients who reported itch as a reason for the visit were more likely to receive an FGA prescription than those who did not (14·7% vs. 4·4%, P < 0·001; see Table 4). In comparison, 3·7% of dermatology patients with a diagnosis of dermatitis or pruritus (vs. 14·3% of PCP patients, P < 0·001), and 7·6% of dermatology patients with itch as the reason for the visit (vs. 14·7% of PCP patients; P = 0·02) were prescribed FGAs.

We then identified 685 (4·0%) PCP office visits by older patients who had at least one diagnosis from the 50 most common dermatologic diagnoses.[16] Of the 5967 visits to dermatology offices, 4206 (70·5%) were by patients who had one of these diagnoses. Using propensity score matching, we matched 637 (93·0%) dermatology and PCP office visits. The rate of FGA prescription at dermatology office visits in the matched sample was lower than that at PCP office visits (3·9% vs. 7·4%; P = 0·02).

Discussion

Older patients received FGA prescriptions at approximately 1·5% of dermatology visits, a prescription rate similar to that for younger patients. Patients were more likely to receive an FGA prescription if one of their presenting symptoms was itch, or if their diagnosis was dermatitis or pruritus. Dermatologists were less likely than PCPs to prescribe an FGA to patients with itch or dermatitis. More specifically, a comparison of PCP and dermatology visits that were similar in patient and visit characteristics suggests that dermatologists were less likely to prescribe FGAs, compared with PCPs in similar clinical circumstances.

Our finding that FGA prescription rates do not differ by age suggests that there is a potential overuse of FGAs among older patients with skin disease. Our findings also show that dermatologists and PCPs differ in their use of FGAs in older patients with skin disease.

Many FGAs are considered 'Potentially Inappropriate Medications' in older adults by the AGS Beers criteria,[4] because of their potential for adverse effects in this patient population. In addition to its well-documented adverse effects on the central nervous system, FGA use is associated with increased risk of injurious falls and fractures in elderly adults, as recently shown in a large systematic review.[20] Although we hypothesized that older patients would have lower rates of FGA prescription because of this, we did not find it to be the case. This is despite the fact that most chronic pruritus is mediated by nonhistaminergic pathways that are not targeted by FGAs.[3] Many older patients with skin disease may therefore be put at risk of adverse events from FGAs, in the absence of evidence that these medications would provide therapeutic benefit.[21]

To put the FGA prescription rate in perspective, it is estimated that, in 2015, at least 433 480 dermatology visits by older patients were associated with an FGA prescription. It is certainly likely that some of these prescriptions were

appropriate and therapeutically useful, with provider and patient balancing risk and benefit. However, we did not find a statistically significant difference between the FGA prescription rate for older patients and that for younger patients, which would be expected if physicians took into account the risks of FGA use in older patients. It therefore appears that dermatologists may not be tailoring their FGA prescription patterns to the unique needs of older patients. This finding is consistent with prior studies showing that patient characteristics are not always taken into account when caring for older patients with skin disease. For example, a patient's life expectancy does not affect the choice of treatment of skin cancer in the U.S.A.[22]

We expected to see differences in FGA prescription rates by sex, because men are more likely to experience urinary side-effects due to antihistamines. Similarly, patients with compromised health are extremely susceptible to the adverse effects of any medication,[23] and we expected to see a lower rate of FGA prescription among patients with a higher number of comorbidities. However, we found no statistically significant differences in FGA prescription rate by sex or number of comorbidities.

PCPs treating older patients with common dermatological conditions prescribed FGAs in 7·4% of visits. This is consistent with previous work using data from NAMCS that showed that a 'high-risk anticholinergic prescription' (including, but not limited to, antihistamines) was prescribed in 6·2% of office visits for older patients.[15] In comparison, dermatologists prescribed FGAs in 3·9% of visits with common dermatological diagnoses and similar patient characteristics. The difference between the FGA prescription rate for dermatologists and that for PCPs is statistically significant; however, there may be clinical reasons that justify this difference. PCPs may be more familiar with their patients' medical history and overall health, and are therefore better able to assess individual needs and the balance of risks and benefits of treatments to individual patients.

Our study has several limitations. Firstly, NAMCS is a cross-sectional survey including a small portion of office visits. Nonetheless, the survey is nationally representative and the largest of its kind in the U.S.A. Secondly, in the early years of data collection, a maximum of eight prescriptions were recorded, but that number increased to 30 by 2015. Thirdly, we have diagnoses recorded by physicians at that visit, but prescriptions can be written without a diagnosis code (e.g. a physician might renew an older FGA prescription). Fourthly, because the dataset does not include the list of all the medications that the patient might be taking at the time of the visit, but only the medications prescribed or renewed at that specific visit, underestimation of FGA prescriptions in our study is therefore possible if patients were already taking medications prescribed by another physician. Finally, a fundamental issue with the anticholinergic side-effects in older patients is the cumulative anticholinergic burden,[24] rather than the anticholinergic effect of a single individual medicine. The NAMCS methodology does not allow for a complete assessment of a patient's anticholinergic burden due to multiple medications.

We hope that collaboration between dermatologists, geriatricians and PCPs can improve the care of older adults with skin disease. We need to increase awareness about the risks of prescribing FGAs to older adults, while at the same time increasing knowledge about alternative, safer, targeted antipruritics. By applying the principles of geriatrics to dermatology, and the principles of dermatology to primary care, we can ultimately better care for all older adults with skin disease.

References

1 Linos E, Chren M, Covinsky K. Geriatric dermatology: a framework for caring for older patients with skin disease. *JAMA Dermatol* 2018; **154**:757–8.
2 Shive M, Linos E, Berger T *et al.* Itch as a patient-reported symptom in ambulatory care visits in the United States. *J Am Acad Dermatol* 2013; **69**:550–6.
3 Berger TG, Shive M, Harper GM. Pruritus in the older patient: a clinical review. *JAMA* 2013; **310**:2443–50.
4 American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015; **63**:2227–46.
5 Campbell N, Boustani M, Limbil T *et al.* The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging* 2009; **4**:225.
6 Gray SL, Anderson ML, Dublin S *et al.* Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med* 2015; **175**:401–7.
7 Doraiswamy PM, Husain MM. Anticholinergic drugs and elderly people: a no brainer? *Lancet Neurol* 2006; **5**:379–80.
8 Ancelin ML, Artero S, Portet F *et al.* Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ* 2006; **332**:455–9.
9 Risacher SL, McDonald BC, Tallman EF *et al.* Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. *JAMA Neurol* 2016; **73**:721–32.
10 Church DS, Church MK. Pharmacology of antihistamines. *World Allergy Organ J* 2011; **4** (Suppl. 3):S22–7.
11 Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey. Available at: http://www.cdc.gov/nchs/ahcd/about_ahcd.htm (last accessed 16 June 2019).
12 Centers for Disease Control and Prevention. Sample National Ambulatory Medical Care Survey 2015 Patient Record. Available at: http://www.cdc.gov/nchs/data/ahcd/2015_NAMCS_PRF_Sample_Card.pdf (last accessed 16 June 2019).
13 Centers for Disease Control and Prevention. NAMCS datasets and documentation. Available at: http://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm (last accessed 16 June 2019).
14 Masnoon N, Shakib S, Kalisch-Ellett L *et al.* What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017; **17**:230.
15 Rhee TG, Choi YC, Ouellet GM *et al.* National prescribing trends for high-risk anticholinergic medications in older adults. *J Am Geriatr Soc* 2018; **66**:1382–7.
16 AAPC. ICD-10: Top 50 codes; Fast forward: 2014 Dermatology. Available at: http://www.stjhs.org/documents/ICD-10/2014_FastForward_Dermatology_Press.pdf (last accessed 16 June 2019).
17 Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci* 2010; **25**:1–21.
18 SAS Software [Computer program]. Version 9.4. Cary, NC: SAS Institute Inc., 2017.

19 Stata Statistical Software [Computer program]. Release 14. College Station, TX: StataCorp LP, 2015.
20 Cho H, Myung J, Suh HS *et al.* Antihistamine use and the risk of injurious falls or fracture in elderly patients: a systematic review and meta-analysis. *Osteoporos Int* 2018; **29**:2163–70.
21 He A, Feldman SR, Fleischer AB. Trends in atopic dermatitis management: comparison of 1990–1997 to 2003–2012. *J Drugs Dermatol* 2018; **17**:135–40.
22 Linos E, Chren M-M, Stijacic Cenzer I *et al.* Skin cancer in US elderly adults: does life expectancy play a role in treatment decisions? *J Am Geriatr Soc* 2016; **64**:1610–15.
23 Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev* 2009; **41**:67–76.
24 Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. *BMC Geriatr* 2015; **15**:31.

5.2. Patient-Reported Measures of Well-Being in Older Multiple Myeloma Patients: Use of Secondary Data Source.

Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-019-01465-3

ORIGINAL ARTICLE

Patient-reported measures of well-being in older multiple myeloma patients: use of secondary data source

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Received: 15 October 2019 / Accepted: 23 December 2019

Abstract

Background Changes in well-being of patients with multiple myeloma (MM) before and after diagnosis have not been quantified.

Aims Explore the use of secondary data to examine the changes in the well-being of older patients with MM.

Methods We used the Health and Retirement Study (HRS), linked to Medicare claims to identify older MM patients. We compared patient-reported measures (PRM), including physical impairment, sensory impairment, and patient experience (significant pain, self-rated health, depression) in the interviews before and after MM diagnosis using McNemar's test. We propensity-matched each MM patient to five HRS participants without MM diagnosis based on baseline characteristics. We compared the change in PRM between the MM patients and their matches.

Results We identified 92 HRS patients with MM diagnosis (mean age = 74.6, SD = 8.4). Among the surviving patients, there was a decline in well-being across most measures, including ADL difficulty (23% to 40%, p value = 0.016), poor or fair self-rated health (38% to 61%, p value = 0.004), and depression (15% to 30%, p value = 0.021). Surviving patients reported worse health than participants without MM across most measures, including ADL difficulty (40% vs. 27%, p value = 0.04), significant pain (38% vs. 22%, p value = 0.01), and depression (29% vs. 11%, p value = 0.003).

Discussion Secondary data were used to identify patients with MM diagnosis, and examine changes across multiple measures of well-being. MM diagnosis negatively affects several aspects of patients' well-being, and these declines are larger than those experienced by similar participants without MM.

Conclusion The results of this study are valuable addition to understanding the experience of patients with MM, despite several data limitations.

Keywords Patient-reported measures · Multiple myeloma · Geriatric assessment · Secondary data use · Rare diseases

Introduction

Multiple myeloma is a rare disease, affecting approximately 7 out of 100,000 persons in the United States each year. Multiple myeloma disproportionately affects older patients, with a median age at diagnosis being over 70 years old [1]. While new treatments are increasing the survival time [2], we know less about the quality of life of older persons who are more susceptible to treatment related adverse events. Older patients are concerned not only with survival time, but also with symptom management, maintaining independence, and how their well-being will be affected by the disease and treatments [3]. Previous studies have shown that patients with multiple myeloma experience higher symptom burden and lower quality of life compared to the general population [4, 5], but these

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Published online: 22 January 2020

studies did not focused on older patients specifically. Overall, there is a consensus that older patients with multiple myeloma could benefit from a geriatric assessment before and during treatment [3, 6, 7]. However, to our knowledge, there have been no studies that formally quantify patient-reported measures in older multiple myeloma patients before and after the diagnosis, or studies comparing the changes in well-being to older adults experiencing the normal ageing process.

As with any rare disease, it can be difficult to recruit large numbers of multiple myeloma patients for research studies due to the low prevalence of the disease, which makes recruiting large numbers of patients resource intensive. One potential source of data for studies of rare diseases is secondary data, including large observational studies and administrative data. In this study we explore studying the well-being of older multiple myeloma patients using Medicare claims data, and Health and Retirement Study (HRS), an ongoing longitudinal study started in 1992. The use of this longitudinal cohort has several advantages. First, due to length of the study period, enough cases accrue over time, creating a feasible study sample. Second, HRS is a detailed study with data on a variety of health status measures that are of interest for older patients. Third, since HRS is a longitudinal study, each surviving participant is interviewed every 2 years, meaning that the measures of interest are observed before and after the diagnosis. Fourth, we can compare changes in the health status measures in HRS participants without multiple myeloma, for whom we have the same health status measures over the same period of time.

The use of HRS data that were not collected for the purpose of learning about well-being of multiple myeloma patients imposes limits on questions that can be answered. For example, since we do not have the information on what treatment the patients receive, we can not determine if well-being changes are due to the disease or its treatment. In addition, because the HRS interviews are biennial, the time between multiple myeloma diagnosis and report of health status measures varies between 0 days and 2 years. However, HRS data also make it possible to address issues that would be difficult in a primary data collection study. It makes it possible to collect data on prediagnosis health status rather than retrospective reports. In addition, we can compare changes in health to population-representative subjects without multiple myeloma.

We conducted this study examining changes before and after multiple myeloma diagnosis with three specific goals: (1) assessing feasibility of using claims data to identify and study patients with multiple myeloma; (2) assessing the change in patient-reported measures before and after diagnosis; (3) comparing the change in patient-reported measures to a comparable sample of individuals without multiple myeloma.

Methods

Participants

The Health and Retirement Study (HRS) was designed to examine changes in health and wealth as people age [8]. It is an ongoing nationally representative longitudinal study of participants age 50 and older. The study started in 1992 and follow up surveys are administered every 2 years. If a participant is not able to complete an interview, the interview is conducted with a proxy respondent.

We examined participants who had a diagnosis of multiple myeloma while enrolled in the HRS, ascertained by linking the HRS survey data to Medicare claims. A participant was identified as having a diagnosis of multiple myeloma if he or she had two or more Medicare claims with ICD9 code 203.0. While we required two claims to confirm the diagnosis of multiple myeloma, the date of diagnosis was set to the date of first claim.

Out of 28,927 HRS participants age 65 or older at any point between 1992 and 2015, 26,044 (90.0%) agreed to have their HRS surveys linked to the Medicare claims. We identified 126 participants who had two or more claims with multiple myeloma. Since we wanted to ensure that the first claim observed in our files was indeed the first diagnosis of multiple myeloma, we excluded 21 (16.7%) participants if they were not enrolled continuously in fee-for-service Medicare for 6 months prior to the first observed claim with multiple myeloma diagnosis. Of the remaining 105 multiple myeloma patients, 13 (12.4%) did not complete a HRS interview within 3 years before a multiple myeloma diagnosis and were, therefore, excluded. This resulted in a sample of 92 multiple myeloma patients included in the study.

Measures

All baseline characteristics of study participants were taken from the last HRS interview before a diagnosis of multiple myeloma. Those included participant characteristics (age, gender, race, marital status, education, wealth, comorbidities, and health behaviors), and patient-reported measures of interest.

We considered nine patient-reported measures that cover a range of well-being for multiple myeloma patients, and are part of geriatric assessment of older patients [9, 10]. The included measures cover the domains that matter most to patients: functioning, sensory impairment, and general well-being. While the nine measures do not constitute together a validated questionnaire, each one of the measures has been validated or used in prior research of

patients' well-being. We include below the exact text of the survey question for each measure, and the justification for the new coding, when the questions were not used in the original form. Additionally, HRS website includes detailed documentation guides for all the measures used in this study [8]. Four measures describe limitations in physical functioning: difficulty in any Activities of Daily Living (ADL), difficulty in any Instrumental Activities of Daily Living (IADL), difficulty walking several blocks, and difficulty climbing one flight of stairs. ADL and IADL measures are standardized measures of assessing function in older adults in both clinical and research setting [11, 12]. Difficulty in any functional measure was assessed in the HRS by asking, "Because of a health or memory problem do you have any difficulty with [activity]?". There were six ADLs (bathing, eating, walking across the room, transferring to and from bed, using toilet, and dressing), and five IADLs (using a phone, preparing hot meals, grocery shopping, managing financing, managing medications) included in the assessment. Next, two sensory impairment measures were included: vision and hearing impairment. Each of the two sensory impairments were assessed by asking, "Is your [hearing/eyesight] excellent, very good, good, fair, or poor using a [hearing aid/glasses or corrective lenses] as usual?". Finally, three additional measures of general well-being were considered: experience of significant pain, self-rated health, and self-reported symptoms of depression. The presence of significant pain was determined using two questions. First, subjects were asked, "Are you often troubled with pain?". Subjects who responded "Yes" were then asked, "How bad is the pain most of the time: mild, moderate or severe?" Subjects who responded "moderate" or "severe" were classified as experiencing significant pain. This classification of significant pain has been applied in previous studies [13, 14], because it reflects the American Geriatrics Society Guidelines for the Pharmacologic Management of Persistent Pain in Older Adults and the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, which both recommend that moderate or severe pain should prompt a clinical response [15, 16]. The SUPPORT study (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) also used this classification to categorize reports of pain at the end of life [17]. Symptoms of depression were measured using the eight-item Center for Epidemiologic Studies Depression Scale [18, 19]. Participants were classified as having symptoms consistent with the diagnosis of depression if they reported more than three symptoms.

The same nine patient-reported measures were also assessed at the first HRS interview after a diagnosis of multiple myeloma.

Statistical analysis

We started with describing the multiple myeloma patients in terms of demographics, socioeconomic status and health status. Next, we assessed the frequency of each patient-reported measure before a multiple myeloma diagnosis. Depression was not assessed for participants with proxy respondents; therefore, 10 patients were not included in the analysis of frequency and changes in depression. Questions about pain levels was not asked in early HRS interviews (1992–1993), so 5 patients were not included in the analyses invlolving significant pain. Analyses were conducted independently for each variable to prevent missing values from one variable affecting the sample size in the analysis of other variables.

Next, we compared the frequency of adverse health on the patient-reported measures before and after a multiple myeloma diagnosis. Only patients that completed the interview after their multiple myeloma diagnosis were included in this analysis, as the goal of this study was to describe well-being and changes in well-being of the patients who survive the initial period after multiple myeloma diagnosis. Patients who died within 2 years of multiple myeloma diagnosis, but completed an HRS interview between their diagnosis and death, were included in the study. The comparison of patients before and after multiple myeloma diagnosis was done using McNemar's test.

Finally, we compared the change in frequency of adverse health on the patient-reported measures between HRS patients with a diagnosis of multiple myeloma to those without the diagnosis over the same time period, i.e., selecting subjects interviewed around the same time. To perform this comparison, we matched each patient with multiple myeloma to five individuals without multiple myeloma. The matching was performed using a mixture of propensity score matching and exact matching. Patients were matched on propensity score for being diagnosed with multiple myeloma, calculated using age, gender, race, marital status, education, wealth, number of comorbidities, and smoking status. Additionally, patients were matched on exact year of interview before and after a diagnosis of multiple myeloma, and on exact status of patient-reported measure for the multiple myeloma patient before the diagnosis. The matching was done separately for each patient-reported measure. This analysis was again limited only those patients who completed the HRS interview after a diagnosis of multiple myeloma, as our goal was to describe the experience among surviving patients.

Statistical analyses were performed using SAS 9.4 [20] and R 3.4 [21, 22] software. This study has been approved by the Center for Disease Control's Institutional Review Board (CDC).

Results

Table 1 describes the prediagnosis baseline characteristics of the multiple myeloma patients included in this study. The mean age of 92 patients was 74.6 (SD = 8.4), and 47% were women. Forty-three percent of patients had 3 or more chronic conditions before diagnosis. The most common ADL difficulties were getting dressed (13%) and bathing (13%). The most common IADL difficulties shopping for groceries (17%) and preparing hot meals (17%). Eighteen patients (20%) died within 1 year, and 38 (41%) died within 2 years of multiple myeloma diagnosis. This mortality rate is comparable to mortality rates reported in other long-term studies of older adults [2, 23]. Of the 92 patients included in the study, 66 (72%) completed HRS interview after multiple myeloma diagnosis. Most subjects not completing an interview died before there scheduled interview. The median time between interview before multiple myeloma diagnosis and the diagnosis was 13.0 months (IQR 6.3–19.1), and the median time between the diagnosis and the first interview after the diagnosis was 12.6 months (6.0–18.0) (Table 1).

Table 1 Baseline characteristics of multiple myeloma patients before diagnosis

Characteristics	*N* (%)
Age	74.6 ± 8.4
Women	43 (47%)
White race	70 (76%)
Married	54 (59%)
Education less than High School	25 (27%)
Wealth (median, IQR)	151 K (45–405 K)
BMI	
≤ 25	31 (34%)
> 25	59 (66%)
Number of comorbidities ≥ 3	40 (43%)
Previous diagnosis of cancer	27 (30%)
Current smoker	6 (7%)
Drinker	41 (45%)
ADL difficulty	
Bathing	12 (13%)
Eating	5 (5%)
Walking across the room	9 (10%)
Transferring to and from bed	8 (9%)
Dressing	12 (13%)
Using toilet	6 (7%)
IADL difficulty	
Using the telephone	6 (7%)
Managing finances	13 (14%)
Managing medications	6 (7%)
Shopping for groceries	15 (17%)
Preparing meals	15 (17%)
Proxy interview	10 (11%)
Months between interview before diagnosis and diagnosis (median, IQR)	13.0 (6.3–19.1)
Months between diagnosis and interview after diagnosis (median, IQR)	12.6 (6.0–18.0)
Died within 1 year of diagnosis	18 (20%)
Died within 2 years of diagnosis	38 (41%)

BMI body mass index, *ADL* activities of daily living, *IADL* instrumental activities of daily living

About a quarter of all multiple myeloma patients reported difficulty with at least one ADL ($n = 22$, 24%) before the diagnosis (Table 2). Twenty-nine patients (32%) reported difficulty with at least one IADL, 34 patients (37%) reported difficulty with walking several blocks, and 25 patients (27%) reported difficulty with climbing one flight of stairs. Vision impairment was reported by 29 patients (32%), and hearing impairment was reported by 20 patients (22%) before multiple myeloma diagnosis. About a quarter of the patients experienced significant pain ($n = 20$, 23%), and about a fifth reported symptoms of depression ($n = 15$, 19%). The most common impairment before multiple myeloma diagnosis was poor or fair self-reported health ($n = 37$, 40%).

Impairments in patient-reported measures in surviving multiple myeloma patients increased significantly after the diagnosis (Table 3). Patients reported higher rates of difficulty in three of the four physical measures, including increases in ADL difficulty (23% to 40%, $p = 0.02$), difficulty walking several blocks (30% to 60%, $p < 0.001$), and difficulty climbing one flight of stairs (25% to 47%, $p = 0.003$). There was no statistically significant change in IADL difficulty (30% to 41%, $p = 0.13$) The rate of depression symptoms doubled after the diagnosis (15% to 30%, $p = 0.02$), and

Table 2 Frequency of impairment on patient reported measures in the interview before multiple myeloma diagnosis

Characteristic	*N* (%)[a]
Physical impairment	
Difficulty with any ADL	22 (24%)
Difficulty with any IADL	29 (32%)
Difficulty with walking several blocks	34 (37%)
Difficulty with climbing one flights of stairs	25 (27%)
Sensory impairment	
Vision Impairment	29 (32%)
Hearing Impairment	20 (22%)
Patient experience	
Significant pain	20 (23%)
Poor self-rated health	37 (40%)
Depression	15 (19%)

[a]Number of missing values for each variable is as follows: Difficulty was any ADL (1). Difficulty with any IADL (2), Difficulty with walking several blocks (1), Difficulty with climbing one flight of stairs (1), Significant pain (6), Depression (11)

Table 3 Frequency of impairment on patient-reported measures in the interviews before and after multiple myeloma (MM) diagnosis, in patients who survived until HRS interview after diagnosis

Characteristic	*N* in comparison	Before MM diagnosis	After MM diagnosis	*p* value
Physical impairment				
Difficulty with any ADL	65	15 (23%)	26 (40%)	0.016
Difficulty with any IADL	64	19 (30%)	26 (41%)	0.127
Difficulty with walking several blocks	63	19 (30%)	38 (60%)	<0.001
Difficulty with climbing one flights of stairs	59	15 (25%)	28 (47%)	0.003
Sensory impairment				
Vision impairment	66	20 (30%)	20 (30%)	1.000
Hearing impairment	66	13 (20%)	22 (33%)	0.039
Patient experience				
Significant pain	64	17 (27%)	24 (38%)	0.090
Poor self-rated health	64	24 (38%)	39 (61%)	0.004
Depression	53	8 (15%)	16 (30%)	0.021

more patients reported poor or fair self-rated health (38% to 61%, $p=0.004$). There was no significant increase in patients experiencing significant pain (27% to 38%, $p=0.09$). There was no change at all in the rates of vision impairment (30% to 30%, $p=1$), but patients reported significant increase in hearing impairment (20% to 33%, $p=0.04$).

Matched HRS participants without a multiple myeloma diagnosis reported lower rates of some patient-reported measures in the interview after the multiple myeloma diagnosis of the patients (Table 4), even though they were matched to have the same level of impairment before the diagnosis. Participants without multiple myeloma reported lower rates in ADL difficulty (40% vs. 27%, $p=0.04$), difficulty walking several blocks (60% vs. 37%, $p<0.001$), and difficulty climbing one flight of stairs (47% vs. 29%, $p=0.005$). There were no statistically significant differences in IADL difficulty (41% vs. 32%, $p=0.21$), vision impairment (30% vs. 26%, $p=0.52$), or hearing impairment (33% vs. 29%, $p=0.44$). Multiple myeloma patients reported higher rates of poor or fair self-rated health (61% vs. 39%, $p=0.001$), depression symptoms (29% vs. 11%, $p=0.003$), and significant pain (38% vs. 22%, $p=0.01$).

Table 4 Change in impairment of patient-reported measures in surviving multiple myeloma (MM) patients and HRS participants without multiple myeloma

Characteristic	Before MM diagnosis	MM patients after diagnosis	HRS participants without MM diagnosis[a]	*p* value
Physical impairment				
Difficulty with any ADL	15 (23%)	26 (40%)	87 (27%)	0.04
Difficulty with any IADL	19 (30%)	26 (41%)	95 (32%)	0.21
Difficulty with walking several blocks	19 (30%)	38 (60%)	119 (37%)	<0.001
Difficulty with climbing one flights of stairs	15 (25%)	28 (47%)	91 (29%)	0.005
Sensory impairment				
Vision impairment	20 (30%)	20 (30%)	87 (26%)	0.52
Hearing impairment	13 (20%)	22 (33%)	94 (29%)	0.44
Patient experience				
Significant pain	17 (27%)	24 (38%)	69 (22%)	0.01
Poor self-rated health	24 (38%)	39 (61%)	128 (39%)	0.001
Depression	6 (13%)	14 (29%)	17 (11%)	0.003

[a]Each multiple myeloma patient was matched to 5 HRS participants without multiple myeloma diagnosis based on age, gender, race/ethnicity, marital status, education, wealth, number of comorbidities, and smoking status (using propensity score for multiple myeloma diagnosis) and exact matching on year of interview before and after diagnosis, and the presence of each patient-reported measures of interest at the interview before the multiple myeloma diagnosis of the patient with multiple myeloma

Discussion

Using Medicare claims data linked to 26,044 HRS subjects, we identified 105 patients with multiple myeloma, 92 of which completed HRS interviews within 3 years of diagnosis. Our study showed that a multiple myeloma diagnosis negatively affects several aspects of patients' well-being. Decline in several, but not all, patient-reported measures was significantly larger among surviving multiple myeloma patients than the changes among similar participants without multiple myeloma diagnosis. These findings have a number of limitations imposed by the nature of the HRS data, yet also provide new insights beyond what is possible with primary data collection.

Health and Retirement Study was not collected for the purpose of learning about multiple myeloma, yet the design and richness of HRS study makes it possible to describe important aspects of the patient experience. While the multiple myeloma sample in our study is not a large sample that allows for multivariate modeling, it is large enough for exploratory analyses and meaningful description of changes in impairments that matter to patients before and after diagnosis of multiple myeloma. We obtained this sample using significantly less resources and time than would be required to recruit the same number of multiple myeloma patients. For example, a primary data collection study that lasted from 2012 to 2015 recruited only 40 older patients [5], while another study recruited 41 adult patients of all ages in 3 months [4]. Furthermore, by leveraging the longitudinal nature of the HRS, our study was able to obtain data on patient-reported measures of interest prior to diagnosis, which would be impossible to obtain using primary data collection. Our study shows that we can use alternative data sources, such as claims data or larger observational studies, to design and perform some basic, but important, health research studies on rare diseases.

Our study indicates significant decline in several patient-reported measures in multiple myeloma patients after diagnosis. First, our study shows that surviving patients experience significant functional decline after the diagnosis, as measured by difficulty with activities of daily living and mobility. Prior studies in older patients with other types of cancer have also shown the functional status declines after cancer diagnoses [24, 25]. While decline in those domains is common in ageing persons, we have also shown that the functional decline in multiple myeloma patients is significantly higher than decline in similar HRS participants without multiple myeloma diagnosis. Our study also shows that there is significant decline in patient well-being, as assessed by pain, self-reported health, and depression. Similar to functional decline, reports of pain, poor or fair self-rated health, and depressive symptoms become more common in surviving multiple myeloma patients after diagnosis than participants without multiple myeloma. These results are analogous to results of another study based on secondary longitudinal data source (English Longitudinal Study of Ageing), which showed that health and well-being of patient with cancer of any type deteriorated more rapidly than health and well-being of similar patient without cancer diagnosis [26]. Our findings are significant, since impairments in well-being can themselves lead to further bad outcomes in older patients [4, 27, 28].

The measures of function and well-being that we considered in this study are rarely targets of therapy in older persons with cancer and seldom used as outcome measures in clinical trials of treatments for myeloma and other cancers. Yet these measures are very important to cancer patients, some of whom view quality of life as a more important outcome than survival. The use of population-based data sources such as the HRS to determine which measures of function and well-being are mostly likely to deteriorate after a cancer diagnosis may be useful in helping designers of cancer treatment trials consider the types of outcome measures that might be included in their trials. Furthermore, both the high mortality rate of multiple myeloma patients (20% 1-year mortality) and the high likelihood of worsening quality of life in patients with multiple myeloma highlights the importance of holistic assessment and appropriate geriatric and palliative care. Palliative care has been recognized as an important part of care for cancer patients [29, 30], where patients' physical, mental, and psychosocial needs need to be addressed in addition to treating the underlying cancer. Unfortunately, a prior study has shown that patients with hematological cancers are less likely to receive palliative care than patients with other cancers [31].

It is important to discuss several issues in this study that can limit the clinical conclusions of this and other studies using this type of secondary data. First, the time between multiple myeloma diagnosis and the interview before the diagnosis varies from 8 days to 34 months. Since patient-reported measures are not always measured immediately before the diagnosis, patient-reported measures might have changed for some patients between the last measurement and multiple myeloma diagnosis. Similarly, the time between the diagnosis and the interview after the diagnosis also varies. The patient-reported measures are likely to change often as the treatments progress, including repeated periods of improvement and decline [6]. Second, we do not have information on the treatments that each patient is receiving, which prevents us from understanding how different treatments affect the outcomes, and when in the treatment cycle the changes occur. Thus, our results further highlight the importance of including this important information about

patient oriented outcomes in observational and clinical studies of cancer therapeutics.

Our study showed that secondary data can be used to identify patients with rare diseases, and perform exploratory and hypotheses generating studies. We showed that patient-reported measures in older adults worsen after multiple myeloma diagnosis, and the decline in surviving multiple myeloma patients is significantly worse than the decline is similar older adults without multiple myeloma. This indicates that older patients could benefit from supportive geriatric and palliative care to help manage the symptoms that worsen with multiple myeloma diagnosis and treatment.

Acknowledgments Open Access funding provided by Projekt DEAL.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Irena Cenzer, Annette Rodriguez, and Kenneth Covinsky. The first draft of the manuscript was written by Irena Cenzer and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding Dr. Kenneth Covinsky is supported by the UCSF Older Americans Independence Center (P30 AG044281).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (UCSF Institutional Review Board (IRB), IRB number 10-00883) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statement of human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Written informed consent was provided by participants before entering the HRS.

References

1. Howlader N, Noone AM, Krapcho M et al (2017) SEER cancer statistics review, 1975-2014. National Cancer Institute, Bethesda, MD
2. Kumar SK, Dispenzieri A, Lacy MQ et al (2014) Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. https://doi.org/10.1038/leu.2013.313
3. Wildes TM, Rosko A, Tuchman SA (2014) Multiple myeloma in the older adult: better prospects, more challenges. J Clin Oncol. https://doi.org/10.1200/JCO.2014.55.1028
4. Kiely F, Cran A, Finnerty D et al (2017) Self-reported quality of life and symptom burden in ambulatory patients with multiple myeloma on disease-modifying treatment. Am J Hosp Palliat Med. https://doi.org/10.1177/1049909116646337
5. Wildes TM, Tuchman SA, Klepin HD et al (2018) Geriatric assessment in older adults with multiple myeloma. J Am Geriatr Soc 67:987–991. https://doi.org/10.1111/jgs.15715
6. King TA, King MT, White KJ (2017) Patient reported outcomes in optimizing myeloma patients' health-related quality of life. Semin Oncol Nurs. https://doi.org/10.1016/j.soncn.2017.05.006
7. Lee SJ (2004) Patient-reported outcomes in multiple myeloma. JNCCN J Natl Compr Cancer Netw. https://doi.org/10.6004/jnccn.2004.0031
8. Health and Retirement Study. http://hrsonline.isr.umich.edu/. Accessed 15 Mar 2019
9. Elsawy B, Higgins KE (2011) The geriatric assessment. Am Fam Physician 83:48–56
10. Mariano J, Min LC (2012) Assessment. In: Naeim A, Reuben DB, Ganz PA (eds) Management of cancer in the older patient. Elsevier, Philadelphia, pp 39–50
11. Katz S, Ford AB, Moskowitz RW et al (1963) Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. JAMA, J Am Med Assoc. https://doi.org/10.1001/jama.1963.03060120024016
12. Hardy SE (2014) Consideration of function and functional decline. In: Williams BA, Chang A, Ahalt C et al (eds) Current diagnosis and treatment: geriatrics, 2nd edn. New York, McGraw-Hill Education
13. Smith AK, Cenzer IS, Knight SJ et al (2010) The epidemiology of pain during the last 2 years of life. Ann Intern Med. https://doi.org/10.7326/0003-4819-153-9-201011020-00005
14. Andrews JS, Cenzer IS, Yelin E et al (2013) Pain as a risk factor for disability or death. J Am Geriatr Soc. https://doi.org/10.1111/jgs.12172
15. Persons AGSP on the PM of PP in O (2009) Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 57:1331–1346. https://doi.org/10.1111/j.1532-5415.2009.02376.x
16. Swarm R, Abernethy AP, Anghelescu DL et al (2010) Adult cancer pain. J Natl Compr Canc Netw 8:1046–1086. https://doi.org/10.6004/jnccn.2010.0076
17. Lynn J, Teno JM, Phillips RS et al (1997) Perceptions by family members of the dying experience of older and seriously ill patients. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Ann Intern Med 126:97–106. https://doi.org/10.7326/0003-4819-126-2-199701150-00001
18. Turvey CL, Wallace RB, Herzog R (1999) A revised CES-D measure of depressive symptoms and a DSM-based measure of major depressive episodes in the elderly. Int Psychogeriatr. https://doi.org/10.1017/S1041610299005694
19. Steffick DE (2000) Documentation of affective functioning measures in the health and retirement study. Institute for Social Research, University of Michigan, Ann Arbor

20. SAS Institute (2016) The SAS system for Windows. Release 9.4. SAS Inst., Cary, NC
21. Ho DE, Imai K, King G et al (2015) MatchIt: nonparametric preprocessing for parametric causal inference. J Stat Softw. https://doi.org/10.18637/jss.v042.i08
22. R Core Team (2017) R: A language and environment for statistical computing. https://www.r-project.org/
23. Costa LJ, Gonsalves WI, Kumar SK (2015) Early mortality in multiple myeloma. Leukemia. https://doi.org/10.1038/leu.2015.33
24. Kenis C, Decoster L, Bastin J et al (2017) Functional decline in older patients with cancer receiving chemotherapy: a multicenter prospective study. J Geriatr Oncol. https://doi.org/10.1016/j.jgo.2017.02.010
25. Decoster L, Kenis C, Schallier D et al (2017) Geriatric assessment and functional decline in older patients with lung cancer. Lung. https://doi.org/10.1007/s00408-017-0025-2
26. Williams K, Jackson SE, Beeken RJ et al (2016) The impact of a cancer diagnosis on health and well-being: a prospective, population-based study. Psychooncology. https://doi.org/10.1002/pon.3998
27. Bruera E, Schoeller T, Wenk R et al (1995) A prospective multicenter assessment of the Edmonton staging system for cancer pain. J Pain Symptom Manag. https://doi.org/10.1016/0885-3924(95)00052-Z
28. Bamia C, Orfanos P, Juerges H et al (2017) Self-rated health and all-cause and cause-specific mortality of older adults: individual data meta-analysis of prospective cohort studies in the CHANCES Consortium. Maturitas. https://doi.org/10.1016/j.maturitas.2017.06.023
29. Zanwar S, Abeykoon JP, Kapoor P (2019) Challenges and strategies in the management of multiple myeloma in the elderly population. Curr Hematol Malig Rep. https://doi.org/10.1007/s11899-019-00500-4
30. Ferrell BR, Temel JS, Temin S et al (2017) Integration of palliative care into standard oncology care: American society of clinical oncology clinical practice guideline update. J Clin Oncol. https://doi.org/10.1200/JCO.2016.70.1474
31. Howell DA, Shellens R, Roman E et al (2011) Haematological malignancy: are patients appropriately referred for specialist palliative and hospice care? A systematic review and meta-analysis of published data. Palliat Med. https://doi.org/10.1177/0269216310391692

6. ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my mentors and colleagues at the Division of Geriatrics at the University of California, San Francisco. I cannot imagine having a better source of support and inspiration during my PhD study than the one provided by the remarkable patience, motivation, and immense knowledge of brilliant researchers and even better people, such as Dr. Ken Covinsky, Dr. Alex Smith, Dr. Sei Lee, Dr. Eleni Linos, and many others.

I would also like to thank my thesis committee: Prof. Helmut Ostermann, Prof. Eva Grill, and Dr. Karin Berger, for their comments and encouragement.

I must acknowledge my four favorite older adults: Dina, Mladen, Pam, and Doug. They are an amazing example to me that there is no age at which one needs to retire from loving, traveling, thinking, and teaching math.

Last but not least, my gratitude and love go to Mike, with whom I am looking forward to spending my elderhood; and to Adam and Nora, my two greatest inspirations. I couldn't and wouldn't have done it without you three.

7. AFFIDAVIT

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Affidavit

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I hereby declare, that the submitted thesis entitled

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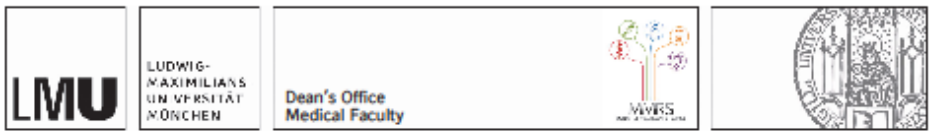

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9. LIST OF ALL SCIENTIFIC PUBLICATIONS TO DATE

1 Kotwal AA, Holt-Lunstad J, Newmark RL, Cenzer I, Smith AK, Covinsky K, Escueta D, Lee J, Perissinotto C. Social Isolation and Loneliness Among San Francisco Bay Area Older Adults During the COVID-19 Shelter-in-Place Orders. J Am Geriatr Soc. [Accepted 2020 Sep 17]

2 Yourman LC, Cenzer I, Boscardin WJ, Nguyen BT, Smith AK, Schonberg MA, Schoenborn NL, Widera EW, Orkaby A, Rodriguez A, Lee SJ. Time to Benefit of Statins for the Primary Prevention of Cardiovascular Events in Adults Age 50-75 years: A Survival Meta-analysis of Randomized Clinical Trials. JAMA Intern Med. [Accepted 2020 Sep 8]

3 Tang VL, Cenzer I, McCulloch CE, Finlayson E, Cooper Z, Silvestrini M, Ngo S, Schmitt EM, Inouye SK. Preoperative Depressive Symptoms Associated with Poor Functional Recovery after Surgery. J Am Geriatr Soc. 2020 Sep 8;. doi: 10.1111/jgs.16781. [Epub ahead of print]

4 Cenzer I, Boscardin WJ, Berger K. Performance of matching methods in studies of rare diseases: a simulation study., Intractable Rare Dis Res. 2020 May 13;9(2):79-88. (DOI: 10.5582/irdr.2020.01016)

5 Kata A, Cenzer I, Sudore RL, Covinsky KE, Tang VL. Advance Care Planning Prior to Death in Older Adults with Hip Fracture., J Gen Intern Med. 2020 May 4. doi:10.1007/s11606-020-05644-1. doi:10.1007/s11606-020-05644-1.

6 Cenzer I, Berger K, Rodriguez AM, Ostermann H, Covinsky KE., Patient-reported measures of well-being in older multiple myeloma patients: use of secondary data source., Aging Clin Exp Res. 2020 JAN 22. doi: 10.1007/s40520-019-01465-3. [Epub ahead of print]

7 Smith GM, Cenzer IS, Covinsky K, Reuben DB, Smith AK., Who Becomes a High Utilizer? A Case-Control Study of Older Adults in the USA., J Gen Intern Med. 2019 Nov 25. doi: 10.1007/s11606-019-05331-w. [Epub ahead of print]

8 Berger K, Staudenmaier T, Cenzer I, Crispin A, Strobach D, Ostermann H., Epidemiology, patient adherence, and costs of oral mucositis in routine care in stem cell transplantation., Support Care Cancer. 2019 Nov 5. doi: 10.1007/s00520-019-05107-2. [Epub ahead of print]

9 Dudley N, Ritchie CS, Stijacic-Cenzer I, Lee SJ., Palliative Care Needs in Oncology, Cardiology, and Neurology Clinic Patients in the USA., J Gen Intern Med. 2019 Jul;34(7):1100-1102. doi: 10.1007/s11606-019-04854-6.

10 Cenzer I, Nkansah-Mahaney N, Wehner M, Chren MM, Berger T, Covinsky K, Berger K, Abuabara K, Linos E., A Multi Year Cross Sectional Study of US National Prescribing Patterns of First

Generation Sedating Antihistamines in Older Adults with Skin Disease., Br J Dermatol. 2019 Apr 25. doi: 10.1111/bjd.18042. [Epub ahead of print]

11 Kanbergs A, Ahalt C, Cenzer IS, Morrison RS, Williams BA., "No One Wants to Die Alone": Incarcerated Patients' Knowledge and Attitudes About Early Medical Release., J Pain Symptom Manage. 2019 Apr;57(4):809-815.

12 Aliberti MJR, Cenzer IS, Smith AK, Lee SJ, Yaffe K, Covinsky KE., Assessing Risk for Adverse Outcomes in Older Adults: The Need to Include Both Physical Frailty and Cognition., J Am Geriatr Soc. 2019 Mar;67(3):477-483.

13 Dudley N, Ritchie CS., Stijacic-Cenzer I, Lee SJ, Palliative Care Needs in Oncology, Cardiology, and Neurology Clinic Patients in the USA., J Gen Intern Med. 2019 Feb 7; Epub

14 Ahalt C, Stijacic-Cenzer I, Miller BL, Rosen HJ, Barnes DE, Williams BA., Cognition and Incarceration: Cognitive Impairment and Its Associated Outcomes in Older Adults in Jail., J Am Geriatr Soc. 2018 Nov;66(11):2065-2071.

15 Wolff JL, Mulcahy J, Roth DL, Cenzer IS, Kasper JD, Huang J, Covinsky KE., Long-Term Nursing Home Entry: A Prognostic Model for Older Adults with a Family or Unpaid Caregiver., J Am Geriatr Soc. 2018 Oct;66(10):1887-1894.

16 Romo RD, Cenzer IS, Williams BA, Smith AK., Relationship Between Expectation of Death and Location of Death Varies by Race/Ethnicity., Am J Hosp Palliat Care. 2018 Oct;35(10):1323-1329.

17 Humphreys J, Ahalt C, Stijacic-Cenzer I, Widera E, Williams B., Six-Month Emergency Department Use among Older Adults Following Jail Incarceration., J Urban Health. 2018 Aug;95(4):523-533.

18 Dudley N, Lee SJ, Stijacic-Cenzer I, Ritchie CS., Prevalence of Multimorbidity Among Older Adults With Advanced Illness Visits to U.S. Subspecialty Clinics., J Pain Symptom Manage. 2018 Jul;56(1):e4-e6.

19 Dudley N, Ritchie CS, Wallhagen MI, Covinsky KE, Cooper BA, Patel K, Stijacic Cenzer I, Chapman SA., Characteristics of Older Adults in Primary Care Who May Benefit From Primary Palliative Care in the U.S., J Pain Symptom Manage. 2018 Feb;55(2):217-225.

20 Jih J, Stijacic-Cenzer I, Seligman HK, Boscardin WJ, Nguyen TT, Ritchie CS., Chronic disease burden predicts food insecurity among older adults., Public Health Nutr. 2018 Jun;21(9):1737-1742.

21 Staudenmaier T, Cenzer I, Crispin A, Ostermann H, Berger K., Burden of oral mucositis in stem cell transplant patients-the patients' perspective., Support Care Cancer. 2018 May;26(5):1577-1584.

22 Greene M, Ahalt C, Stijacic-Cenzer I, Metzger L, Williams B., Older adults in jail: high rates and early onset of geriatric conditions., Health Justice. 2018 Feb 17;6(1):3.

23 Bleijenberg N, Smith AK, Lee SJ, Cenzer IS, Boscardin JW, Covinsky KE., Difficulty Managing Medications and Finances in Older Adults: A 10-year Cohort Study., J Am Geriatr Soc. 2017 Jul;65(7):1455-1461

24 Greysen SR, Stijacic Cenzer I, Boscardin WJ, Covinsky KE., Functional Impairment: An Unmeasured Marker of Medicare Costs for Postacute Care of Older Adults., J Am Geriatr Soc. 2017 Sep;65(9):1996-2002

25 Meisel K, Arnold RM, Stijacic Cenzer I, Boscardin J, Smith AK., Survival, Functional Status, and Eating Ability After Percutaneous Endoscopic Gastrostomy Tube Placement for Acute Stroke., J Am Geriatr Soc. 2017 Aug;65(8):1848-1852.

26 Brown RT, Ahalt C, Rivera J, Stijacic Cenzer I, Wilhelm A, Williams BA., Good Cop, Better Cop: Evaluation of a Geriatrics Training Program for Police., J Am Geriatr Soc. 2017 Aug;65(8):1842-1847.

27 Sheffrin M, Stijacic Cenzer I, Steinman MA., Desire for predictive testing for Alzheimer's disease and impact on advance care planning: a cross-sectional study., Alzheimers Res Ther. 2016 Dec 13; 8(1):55

28 Bolano M, Ahalt C, Ritchie C, Stijacic-Cenzer I, Williams B., Detained and Distressed: Persistent Distressing Symptoms in a Population of Older Jail Inmates., J Am Geriatr Soc. 2016 Nov;64(11):2439-2355

29 Ritchie CS, Kelley AS, Stijacic Cenzer I, Smith AK, Wallhagen ML, Covinsky KE., High Levels of Geriatric Palliative Care Needs in Hip Fracture Patients Before the Hip Fracture., J Pain Symptom Manage. 2016 Oct; 52(4):533-538

30 Tang VL, Sudore R, Cenzer IS, Boscardin WJ, Smith A, Ritchie C, Wallhagen M, Finlayson E, Petrillo L, Covinsky K., Rates of Recovery to Pre-Fraction Function in Older Persons with Hip Fracture: an Observational Study., J Gen Intern Med. 2017 Feb;32(2):153-158

31 Cenzer IS, Tang V, Boscardin WJ, Smith AK, Ritchie C, Wallhagen MI, Espaldon R, Covinsky KE., One-Year Mortality After Hip Fracture: Development and Validation of Prognostic Index. , J Am Geriatr Soc. 2016 Sep;64(9):1863-8

32 Linos E, Chren MM, Stijacic Cenzer I, Covinsky KE., Skin Cancer in US Elderly Adults: Does Life Expectancy Play a Role in Treatment Decisions?., J Am Geriatr Soc. 2016 Aug;64(8):1610-5

33 Smith AK, Cenzer IS, John Boscardin W, Ritchie CS, Wallhagen ML, Covinsky KE., Increase in Disability Prevalence Before Hip Fracture., J Am Geriatr Soc. 2015 Oct;63(10):2029-35

34 Lee SJ, Stijacic-Cenzer I, Barnhart C, McClymont K, Steinman MA., Changing Patterns of Glucose-Lowering Medication Use in VA Nursing Home Residents With Diabetes, 2005 to 2011., J Am Med Dir Assoc. 2015 Oct 1;16(10):898.e9-898.e14.

35 Greene M, Covinsky KE, Valcour V, Miao Y, Madamba J, Lampiris H, Cenzer IS, Martin J, Deeks SG., Geriatric Syndromes in Older HIV-Infected Adults., J Acquir Immune Defic Syndr. 2015 Jun 1;69(2):161-7.

36 Tang V, Boscardin WJ, Stijacic-Cenzer I, Lee SJ., Time to benefit for colorectal cancer screening: survival meta-analysis of flexible sigmoidoscopy trials., BMJ. 2015 Apr 16;350:h1662. Erratum in: BMJ. 2015;350:h2228.

37 Greysen SR, Stijacic Cenzer I, Auerbach AD, Covinsky KE., Functional impairment and hospital readmission in Medicare seniors., JAMA Intern Med. 2015 Apr;175(4):559-65.

38 Hsu A, Conell-Price J, Stijacic Cenzer I, Eng C, Huang AJ, Rice-Trumble K, Lee SJ., Predictors of urinary incontinence in community-dwelling frail older adults with diabetes mellitus in a cross-sectional study., BMC Geriatr. 2014 Dec 16;14:137.

39 Lee SJ, Ritchie CS, Yaffe K, Stijacic Cenzer I, Barnes DE., A clinical index to predict progression from mild cognitive impairment to dementia due to Alzheimer's disease. PLoS One. 2014 Dec 8;9(12):e113535

40 Williams BA, Ahalt C, Stijacic-Cenzer I, Smith AK, Goldenson J, Ritchie CS., Pain Behind Bars: The Epidemiology of Pain in Older Jail Inmates in a County Jail., J Palliat Med. 2014 Dec; 17(12):1336-43

41 Chodos AH, Ahalt C, Cenzer IS, Myers J, Goldenson J, Williams BA., Older jail inmates and community acute care use., Am J Public Health. 2014 Sep;104(9):1728-33.

42 Greysen SR, Chin Garcia C, Sudore RL, Cenzer IS, Covinsky KE., Functional impairment and Internet use among older adults: implications for meaningful use of patient portals., JAMA Intern Med. 2014 Jul;174(7):1188-90.

43 Barnes DE, Cenzer IS, Yaffe K, Ritchie CS, Lee SJ., A point-based tool to predict conversion from mild cognitive impairment to probable Alzheimer's disease., Alzheimers Dement. 2014 Feb 1. pii: S1552-5260(13)02941-5.

44 Covinsky KE, Cenzer IS, Yaffe K, O'Brien S, Blazer DG., Dysphoria and anhedonia as risk factors for disability or death in older persons: implications for the assessment of geriatric depression., Am J Geriatr Psychiatry. 2014 Jun;22(6):606-13.

45 Andrews JS, Cenzer IS, Yelin E, Covinsky KE., Pain as a risk factor for disability or death., J Am Geriatr Soc. 2013 Apr;61(4):583-9.

46 Cruz M, Covinsky K, Widera EW, Stijacic-Cenzer I, Lee SJ., Predicting 10-year mortality for older adults., JAMA. 2013 Mar 6;309(9):874-6.

47 Lee SJ, Boscardin WJ, Stijacic-Cenzer I, Conell-Price J, O'Brien S, Walter LC., Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark., BMJ. 2013 Jan 8;346:e8441

48 Perissinotto CM, Stijacic Cenzer I, Covinsky KE., Loneliness in older persons: a predictor of functional decline and death., Arch Intern Med. 2012 Jul 23;172(14):1078-83. Arch Intern Med. 2012 Jul 23;172(14):1078-83.

49 Yau CK, Eng C, Cenzer IS, Boscardin WJ, Rice-Trumble K, Lee SJ., Glycosylated hemoglobin and functional decline in community-dwelling nursing home-eligible elderly adults with diabetes mellitus., J Am Geriatr Soc. 2012 Jul;60(7):1215-21.

50 Chen B, Covinsky KE, Stijacic Cenzer I, Adler N, Williams BA., Subjective social status and functional decline in older adults., J Gen Intern Med. 2012 Jun;27(6):693-9.

51 Smith AK, McCarthy E, Weber E, Cenzer IS, Boscardin J, Fisher J, Covinsky K., Half of older Americans seen in emergency department in last month of life; most admitted to hospital, and many die there., Health Aff (Millwood). 2012 Jun;31(6):1277-85.

52 Sun VK, Stijacic Cenzer I, Kao H, Ahalt C, Williams BA., How safe is your neighborhood? Perceived neighborhood safety and functional decline in older adults., J Gen Intern Med. 2012 May;27(5):541-7.

53 Lee SJ, Boscardin WJ, Stijacic Cenzer I, Huang ES, Rice-Trumble K, Eng C., The risks and benefits of implementing glycemic control guidelines in frail older adults with diabetes mellitus., J Am Geriatr Soc. 2011 Apr;59(4):666-72.

54 Smith AK, Cenzer IS, Knight SJ, Puntillo KA, Widera E, Williams BA, Boscardin WJ, Covinsky KE., The epidemiology of pain during the last 2 years of life., Ann Intern Med. 2010 Nov 2;153(9):563-9.

55 Kelly A, Conell-Price J, Covinsky K, Cenzer IS, Chang A, Boscardin WJ, Smith AK., Length of stay for older adults residing in nursing homes at the end of life., J Am Geriatr Soc. 2010 Sep;58(9):1701-6.

56 Williams BA, McGuire J, Lindsay RG, Baillargeon J, Cenzer IS, Lee SJ, Kushel M., Coming home: health status and homelessness risk of older pre-release prisoners., J Gen Intern Med. 2010 Oct;25(10):1038-44.