REVIEW

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Geriatric update 2022: Preventing Alzheimer disease and more

ABSTRACT

Articles published in 2020 and 2021 contain important research related to preventing Alzheimer dementia; the relationships between frailty, social isolation, and mortality; COVID-19 risks in patients with dementia; hospital-at-home programs; deprescribing antihypertensive drugs; bisphosphonate-related atypical femoral fractures; and cannabis use in older adults.

KEY POINTS

Factors that seem to protect against Alzheimer dementia include aggressive cardiovascular risk-factor modification (best applied at midlife, with diminishing returns after age 75), good sleep, regular physical exercise, cognitively stimulating activities, avoidance of head trauma, and timely intervention for depression—but not aspirin in low daily doses.

Patients with dementia are at increased risk for SARS-CoV-2 infection, and Black patients with dementia are more likely to be infected than White patients with dementia.

Dementia is an independent risk factor for morbidity and mortality in COVID-19.

Deprescribing 1 antihypertensive medication in older adults taking multiple blood pressure medications is not associated with significant changes in blood pressure control.

The risk of atypical femur fractures with bisphosphonate use is much lower than the benefits in fracture reduction.

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PREVENTIVE HEALTH IN OLDER ADULTS

Ellen is a 65-year-old retiree with hypertension that is well controlled on medications. She takes aspirin and a statin for "good health." Ellen's mother has Alzheimer dementia, and Ellen is concerned about her own risk of developing it and asks, "What should I be doing to minimize my risk? Are my medicines helping with this?"

Evidence-based prevention of Alzheimer dementia

Yu et al[1] conducted a large systematic review and meta-analysis grading the evidence for risk factors and preventive measures for Alzheimer dementia. Included in the analysis were 243 prospective observational studies and 153 randomized controlled trials, representing a multiethnic population across 5 continents. Of the patients, 82% were free of dementia at baseline.[1]

From analyses of 134 factors came 21 evidence-based recommendations, all carrying levels of evidence of either A (high) or B (intermediate); 19 were strong recommendations while 2 were negative, ie, not recommended. All 21 recommendations are either level A or B, and 19 were rated as strong, with 2 rated not recommended. Of the 19, notable recommendations include weight loss for adults under 65 (with avoidance of weight loss for those over 65), regular physical and cognitive exercise, avoidance of metabolic disease (diabetes, hypertension) via lifestyle, and preservation of restful sleep and mental health. Recommendations also include close cognitive monitoring for patients with diabetes, weight loss in older age, cerebral athero-

sclerosis or microbleeding, orthostatic hypotension, and depression. This meta-analysis concludes recommending against routine use of estrogen replacement in postmenopausal women and acetylcholinesterase inhibitors for prevention of Alzheimer dementia.[1]

Protective factors include aggressive cardiovascular risk-factor modification (which seems to have the most impact in midlife, with diminishing returns beyond age 75), good-quality sleep, timely intervention for depression, avoidance of head trauma, regular physical exercise, education in early life, and continuing cognitively stimulating activities.

There is strong support for deprescribing aspirin in adults older than 70 who are taking it for primary prevention

This meta-analysis does not say exactly how much sleep, exercise, and cognitively stimulating activity patients should get. However, the 2019 World Health Organization Risk Reduction of Cognitive Decline and Dementia guidelines[2] recommend at least 150 minutes of moderate aerobic activity per week and resistance training at least twice per week. Also, studies in the United States have demonstrated a higher risk of dementia in people who slept 5 or fewer hours per night in midlife and early older adulthood, suggesting the optimal duration of sleep for cognitive health is 7 to 8 hours per night.[3]

Comment. Providers can help patients tailor prevention efforts to their individual needs and stage of life.

Aspirin does not appear to prevent cognitive decline

Ryan et al[4] published a secondary analysis of the ASPREE (Aspirin in Reducing Events in the Elderly) randomized controlled trial, looking specifically at aspirin use and the development of cognitive impairment. ASPREE[5] was a 4.7-year, double-blind, placebo-controlled trial in 19,114 healthy community-dwelling adults age 70 and older from the United States and Australia. They were divided into 2 groups, receiving either daily low-dose aspirin (100 mg/day) or placebo. All patients in the aspirin group were newly initiated on low-dose aspirin for the study.

The original ASPREE trial found no difference in disability-free survival and an increased risk of intracerebral hemorrhage in the aspirin group.[5] The secondary analysis by Ryan et al was done to test the hypothesis that aspirin for cardiovascular primary prevention could reduce the risk of cognitive impairment.[4]

All patients underwent cognitive screening with the Modified Mini-Mental State Examination at enrollment and every other year starting at year 1 by trained study staff. In response to any of 4 cognitive "triggers"—a positive screening test, report of memory concerns, new formal dementia diagnosis, or a new prescription for an acetylcholinesterase inhibitor—they then underwent brain imaging, laboratory tests, and review of clinical notes from their providers. All this information was reviewed by a blinded panel of dementia specialists, and each case was adjudicated as being either probable Alzheimer dementia, possible Alzheimer dementia, mild cognitive impairment, or other cognitive decline or change.

There was no difference in the incidence of Alzheimer dementia, mild cognitive impairment, or other cognitive decline between those taking low-dose aspirin or placebo at 7 years of follow-up.[4] Athough longer follow-up may have captured more cases of cognitive impairment, we believe that 7 years should have been sufficient to see a difference in cognitive outcomes. Subgroup analyses based on demographics and comorbid conditions also showed no difference in any cognitive outcomes. However, the absolute incidences of dementia and mild cognitive impairment in this cohort were lower than had previously been reported in other observational studies.

Comment. This study demonstrated that low-dose daily aspirin does not affect the risk of Alzheimer dementia, mild cognitive impairment, or other cognitive decline. These results are in line with those of other randomized controlled trials and meta-analyses.[6,7] Previous observational studies suggested that low-dose aspirin had a protective effect, but randomized controlled trials have not borne this out. Coupled with the original ASPREE results showing that aspirin did not prolong disability-free survival and led to a higher rate of major hemorrhage than with placebo, there is strong support for deprescribing aspirin in adults over age 70 who are taking it for primary prevention.

Statins for primary prevention: Time needed to treat

Yourman et al[8] performed a meta-analysis of 8 studies and 65,383 participants from the original major studies of statins for primary prevention of major adverse cardiovascular events (MACEs), extracting data on how long it takes to see a benefit in adults ages 50 to 75. It is well established that statins prevent MACE in this age group, but the time to benefit was not known. Time to specific absolute risk reduction was obtained from statistical simulations.

This was independent of low-density lipoprotein cholesterol levels achieved.

The time needed to prevent 1 MACE in 100 patients treated with a statin was 2.5 years, varying across individual study populations. The time needed to prevent 1 MACE in 200 people was 1.3 years, and for 500 people it was 0.8 years. The benefit of statin therapy increased with longer follow-up: for 100 people treated with a statin for primary prevention, 0.3 MACEs were prevented at 1 year, 1.3 at 3 years, and 2.5 by 5 years. Statins did not affect all-cause mortality rates.[8]

Comment. This study provides important information to help guide discussions on the risks and benefits of statin therapy for primary prevention. For those with frailty or life-limiting conditions in midlife to later life, the lag time to benefit from statins for primary prevention may not support their use.

What does this mean for Ellen?

Ellen's use of medications to control her blood pressure and prevent cardiovascular disease in midlife helps reduce her risk of Alzheimer dementia. Incorporating more exercise and mentally stimulating activities into her routine and maintaining good sleep and mental health would further reduce her risk. She is an excellent candidate for aspirin deprescribing to reduce her risk of bleeding, since it has no impact on her risk of developing Alzheimer dementia later in life.

SOCIAL ISOLATION, LONELINESS, AND THE COVID-19 PANDEMIC

Esther is an 87-year-old African American woman with dementia who lives in assisted living. During the first 6 months of the COVID-19 pandemic, her daughter was not allowed to visit her at all. The assisted living facility had 2 outbreaks of the virus, and Esther became much more withdrawn. Her daughter notes, "She's just a shell of herself. So many of her friends have died this year, and it seems like her community and people with dementia have been affected much more." What have been the consequences of COVID-19 pandemic on older adults?

Many older adults experienced 2 pandemics: the disease itself, and the social isolation due to the lockdowns and shelter-in-place orders imposed to control the spread of the virus. This was particularly true of older adults in long-term care settings and those with dementia.

Social isolation during shelter-in-place orders

Kotwal et al[9] examined the impact of social isolation and loneliness in older adults during shelter-in-place orders in a longitudinal study in San Francisco, CA. The researchers telephoned the participants (patients in an academic medical center outpatient and home-based geriatrics setting and at 2 community sites) every 2 weeks from March 2020 to June 2020 and administered a survey.

Loneliness was measured by asking participants if their loneliness was "worse," "about the same," or "better" due to COVID-19, and was graded in severity using the validated 3-item UCLA Loneliness Scale (range 0–6 points; 3+ categorized as high loneliness). Social support was measured using the Modified Duke Social Support Index social interaction subscale (range 0–17; with 6 or less categorized as socially isolated).[9] This scale measures the number of local contacts a person feels close to or can depend on, the frequency of participation in community activities in the past week, and the frequency of social interaction by telephone, video, internet, or in person.

Many older adults experienced 2 pandemics: the disease itself, and the social isolation due to lockdowns and shelter-in-place orders to control spread of the virus

The researchers reached 151 community-dwelling older adults, with an overall response rate of 40%.[9] Their mean age was 75, 65% were female, 8% were Black, and 8% were Asian. Overall, 64% of participants lived alone, and many had significant functional impairment, with 50% reporting hearing or vision impairment and 26% reporting difficulty bathing.

The most common form of social interaction was by telephone, with 43% of participants reporting daily telephone socialization. In contrast, there was much less video-based or Internet-based socializing, with 46% of participants reporting no video-based socialization at all and 26% reporting no Internet-based socializing.[9]

Overall, 40% of older adults had social isolation and few social interactions, and 54% had worsened loneliness due to the pandemic. Notably, loneliness levels remained stable or improved from March to June 2020. This suggests resilience and an ability to adapt in many older adults. However, a notable subset experienced persistent or worsened loneliness over time. In these participants, loneliness was strongly associated with worsening of depression and anxiety and worries about coronavirus and general health.

Combined effects of frailty and social isolation or loneliness

Frailty is a well-known predictor of death in older adults, and loneliness itself is associated with increased morbidity and mortality. But what if you have both?

Hoogendijk et al[10] examined the combined impact of frailty and loneliness or social isolation on mortality as part of the larger Longitudinal Aging Study in Amsterdam, The Netherlands. This cohort study followed 1,427 community-dwelling adults age 65 and older for 22 years (1995–2017). Frailty was measured with the Fried criteria: weight loss, low grip-strength, exhaustion, slow gait-speed, and low physical activity. The respondents completed a medical interview with questions about loneliness and social isolation.

The overall prevalence of frailty was 13%.[10] There was substantial overlap between frailty, loneliness, and social isolation, though 43% of the sample had none of these conditions. However, 5.9% of respondents were frail and lonely, and 6.2% were frail and socially isolated.

As expected, older adults who were frail had a higher risk of death than people without any of the conditions (hazard ratio range 1.40–1.48, $P < .01$ in 2 different analyses). However, frailty combined with loneliness or social isolation conferred the highest risk of death. In those who were frail and lonely, the hazard ratio was 1.83 (95% confidence interval 1.42–2.37); for those who were frail and socially isolated it was 1.77 (95% confidence interval 1.36–2.30) compared with people without any of these conditions.[10]

Comment. This study demonstrated that frailty by itself is associated with increased mortality risk, and frailty in combination with either loneliness or low social support further increases mortality. This is a call to action for extra attention and interventions in this vulnerable group of older adults, including outreach to reduce social isolation.

COVID-19 and dementia

The toll of the COVID-19 pandemic on older adults has been devastating, but it has been catastrophic on those with dementia. There are many reasons why the risk of COVID-19 would be different for people with dementia, including difficulty complying with preventive measures such as hand-washing, mask-wearing, and social distancing, due to cognitive impairment. Many older adults with dementia live in high-risk settings such as assisted living or memory care facilities or have visiting home health workers, and thus are at greater risk of exposure to the virus. Additionally, many people with dementia require hands-on care for their essential activities of daily living such as bathing, in which social distancing is impossible.

Wang et al[11] sought to document if people with dementia are at higher risk of contracting COVID-19 and to quantify that increased risk. Additionally, they examined risk of adverse outcomes and death due to COVID-19 in people with dementia and examined disparities by age, sex, and race.

This case-control study, conducted in August 2020, used de-identified, standardized electronic health record data from the IBM Watson Health Explorys database, which includes data from 61 million adult patients (20% of the US population), 360 hospitals, and 317,000 providers across all 50 US states. Cases and controls were identified as of August 21, 2020, which was the first wave of the pandemic, before vaccines were developed. From this large database, they identified 1 million patients with dementia, 15,770 with COVID-19, and 810 with both dementia and COVID-19.[11]

Patients with dementia had a significantly higher risk of COVID-19 compared with people without dementia (adjusted odds ratio 2.00, 95% confidence interval 1.94–2.06, $P < .001$), after accounting for age, sex, race, comorbidities, or having a nursing home stay. Strikingly, there was a significant racial disparity, with Black patients with dementia more likely to have COVID-19 than White patients with dementia (adjusted odds ratio 2.86, 95% confidence interval 2.67–3.062, $P < .001$).[11]

The risks of morbidity and death with COVID-19 were also increased in patients with dementia. In patients with COVID-19 and dementia, 59% were hospitalized, compared with 23% of COVID-19 patients without dementia ($P < .001$). The rate of hospitalization was also higher in Black patients (73%) than in Whites (54%; $P < .01$). The 6-month mortality rate for patients with COVID-19 and dementia was 21%, compared with 4.8% ($P < .001$) in those without dementia.[11]

This study demonstrates that patients with dementia have substantially higher risks of contracting COVID-19 and dying of it. Of note, this study was conducted in August 2020, before any COVID vaccine was available. While the current widespread availability of vaccines may temper the high mortality rate somewhat, differential rates of vaccination by race may still lead to disparities in severe illness and mortality from COVID. Additionally, the current variants of the SARS-CoV-2 virus are more easily transmissible, even among vaccinated individuals.

Comment. This study highlights the need for public health level solutions to improve dementia care, address racial disparities, and ensure equitable access to vaccines in both the general population and in long-term care settings to reduce the risk in vulnerable older adults with dementia.

What does this mean for Esther?

The great toll of the pandemic that Esther's daughter noticed is real. People with dementia, such as Esther and others in her assisted living facility, had much higher risks of contracting COVID-19 and dying of it than those without dementia. Getting vaccinated, including getting booster doses, is the best way for Esther to reduce her risk of getting severely ill or dying from COVID-19.

SHIFTING HEALTH CARE TO THE HOME

Robert is an 83-year-old man who was admitted to the hospital for community-acquired pneumonia. Before his hospitalization, he could walk with a cane. After several days in the hospital, he was having difficulty with transfers and was discharged to a rehabilitation facility. He reports feeling depressed after being unable to see his family for almost 1 month due to COVID-19 visitation restrictions and wishes he could have received his care at home. Could his hospital and postacute rehabilitation care have been provided in the home?

Hospitalized older adults are at risk of functional decline and complications such as delirium, falls, incontinence, and pressure ulcers.[12] The COVID-19 pandemic has accelerated the shift of healthcare services away from the hospital and other healthcare settings to the home, driven by patient and family desire for in-home care, the expansion of telehealth, and changes in reimbursement.

In November 2020, the Centers for Medicare & Medicaid Services implemented a waiver program that reimburses home-hospital services at the same rate as in-hospital services, leading to an increase in hospital-at-home programs.[13] The waiver is in effect for the duration of the COVID-19 public health emergency. A bipartisan bill has been introduced in both the US Senate and the House of Representatives that, if passed, would extend the acute hospital care at home waiver.[14]

Hospital at home

Levine et al[15] conducted a randomized controlled trial comparing hospital-level care at home and traditional hospital care. The primary outcome was the cost of the acute care episode.

Eligible participants were age 18 or older, lived within the catchment area, had capacity to consent, and had a primary diagnosis of one of several prespecified conditions, including any infection or exacerbation of congestive heart failure, asthma, or chronic obstructive pulmonary disease. Exclusion criteria were residing in a nursing home, high risk for clinical deterioration, need for advanced imaging or procedure, need for routine administration of controlled substances, or need for the assistance of more than 1 person to reach the bedside commode.[15]

They enrolled 91 patients, with a median age of 80 in the home group and a median age of 72 in the hospital group. Participants in the home group received at least 1 daily physician visit and 2 daily registered nurse visits, along with additional visits or services as needed (eg, home health aide, physical therapy). Participants in the control group received usual care in the hospital.

Acute inpatient-level care can be safely provided in the home at lower cost, with better patient outcomes and lower readmission rates

The adjusted mean cost of the acute care episode was 38% lower in the home group than in the hospital group ($P < .001$). The home patients underwent less imaging (14% of patients vs 44%), they had fewer laboratory orders per admission (3 vs 15), and they had fewer consultations (2% of patients vs 31%). None of the home patients were transferred back to the hospital during the acute care episode. Home patients had lower 30-day readmission rates (7% vs 23%). Home patients were less sedentary (12% vs 23% of the day) and spent a lower percentage of the day lying down (18% vs 55%).[15]

In a qualitative evaluation of the study, home patients described better continuity of care, positive experiences with technology, and more factors promoting healing, including environmental comfort, better sleep, and more physical activity.[16]

A limitation of this study was that it was stopped early by the supporting institution to increase the capacity of their home hospital program after interim positive results, resulting in a smaller sample size and limited ability to assess secondary outcomes. The study was conducted with a small number of home physicians at 2 sites within a single healthcare system, which may limit its generalizability. Another notable limitation of the study was that 63% of eli-

gible patients did not enroll in it, largely because the patient or family declined to participate.[16] This differs from other hospital-at-home studies, in which the acceptance rates were over 60%.[17,18]

Saenger et al[19] evaluated reasons patients agreed or declined to participate in a hospital-at-home program. In their study, 66.7% accepted hospital-at-home care, and those who accepted were older and more likely to be female and have Medicaid or dual-eligible status. Reasons for accepting hospital-at-home care included being more comfortable at home (78%), liking having family around (41%), and being able to do things at home (36%). Of those who declined hospital-at-home care, 35% did not give a specific reason, 15% preferred to receive care in the hospital, and 13% were concerned that hospital-at-home care would be insufficient to meet their care needs.[19]

Comments. The randomized controlled trial by Levine et al[15] adds to the growing literature demonstrating that acute inpatient-level care can be safely provided in the home at lower cost with better patient outcomes, including lower readmission rates. Previous studies have shown higher patient and family satisfaction with hospital-at-home, lower rates of delirium, and fewer admissions to skilled nursing facilities after hospitalization.[17,18,20]

Post-acute rehabilitation at home

Augustine et al[21] conducted a single-arm retrospective review of patients participating in a rehabilitation-at-home program. Their intervention was a 30-day bundle including an active phase of home-based medical and rehabilitation services typically delivered in a skilled nursing facility and a transitional phase of care coordination. Primary outcome measures were functional mobility and global function. There were 237 participants, with a 89% rate of acceptance and a mean age of 84.2

Average length of stay in the active phase was 14.2 days, and 55% of patients fully or almost fully met their highest functional goal. The hospital readmission rate was 20% within 30 days. Notably, 87.3% of participants were still living at home at 30 days.[21]

The most significant limitation of this study was that it was a single-arm study and did not directly compare rehabilitation at home with postacute skilled nursing facility or home healthcare, although as noted the readmission and mortality rates were comparable.

Comment. This study showed that rehabilitation at home is feasible and desired by patients, but further studies are necessary to evaluate quality outcomes and cost.

What does this mean for Robert?

Robert would have qualified for hospital at home with his diagnosis of community-acquired pneumonia, receiving his care in his home and not being separated from his family. He would have been less likely to require skilled nursing facility placement for rehabilitation.

Although there are an increasing number of hospital-at-home programs, they are not available in all areas. As of September 30, 2022, Centers for Medicare & Medicaid Services has approved 256 hospitals in 37 states to provide acute hospital care at home under the waiver.[22]

MEDICATIONS AND OLDER ADULTS

An 81-year-old woman with hypertension and osteoarthritis presents to establish care. She was recently hospitalized due to a hip fracture, which she feels occurred because she was light-headed. Her son is with her and is concerned about his mother's medication regimen, which includes lisinopril, amlodipine, hydrochlorothiazide, rosuvastatin, and acetaminophen with oxycodone. He also asks about whether she should take bone-strengthening medications because of the hip fracture, but the patient has expressed unwillingness in the past due to the risk of the femur fractures she has read about in the news.

Deprescribing antihypertensive drugs

Sheppard et al,[23] in a British study in adults age 80 or older who were taking more than 1 antihypertensive medication, found that eliminating 1 medication did not substantially change the target mean systolic blood pressure less than 150 mm Hg after 12 weeks of follow-up. The study excluded those with a history of heart failure due to left ventricular dysfunction, myocardial infarction, or stroke in the preceding 12 months, secondary hypertension, or inability to consent. The study included 569 participants (48.5% women, mean age 84.8), chosen by their primary care providers as likely able to benefit from deprescribing.

Participants were randomized to the 1-drug reduction arm or to usual care. An algorithm for the order of reduction was provided (first calcium channel blockers, then angiotensin-converting enzyme inhibitors, then thiazide diuretics), but the practitioner was not bound by the algorithm. If a beta-blocker or alpha-blocker was to be eliminated, the suggestion was to reduce it gradually.

Sixty-six percent of participants were able to complete this unblinded prospective study. At baseline, the mean systolic blood pressure was 129.4 mm Hg in the reduction group and 130.5 mm Hg in the usu-

al-care group. At the end of 12 weeks, this had risen to 133.7 mm Hg in the reduction group and 130.8 mm Hg in the usual-care group (P = .005), but without clear clinical significance. As for the primary outcome, 86.4% of the patients in the reduction group and 87.7% of those in the usual-care group still had blood pressure lower than 150 mm Hg; the difference was not statistically significant.[23]

The study length was short, and the authors emphasized that this was a noninferiority trial in a very old population and that long-term outcomes should be analyzed in future studies.[23]

Bisphosphonates and risk of atypical femur fracture

Clinicians and patients are often concerned about the risk of atypical fractures associated with the use of bisphosphonates.

Black et al[24] used data from patients enrolled in Kaiser Permanente of Southern California to determine the rate of atypical femur fractures in women who used bisphosphonates for any length of time between January 1, 2007, and November 30, 2017. The database included 196,129 women. They discovered 277 atypical femur fractures, for an overall rate of 0.0014%. Exposure ranged from 3 months to over 8 years.

The highest atypical femoral fracture rate (13.1 per 10,000 patient-years) was in those who took a bisphosphonate for more than 8 years. Of those who took bisphosphonates between 5 and 8 years, the rate was 6.04 per 10,000 patient-years. Asian women were at a higher risk than White women (5.95 vs 1.09 per 10,000 patient-years), although the risk was still low. The risk of atypical femur fracture decreased precipitously at 3 months after discontinuation and remained low thereafter.[24]

This study showed that the absolute risk of atypical femur fracture was very low compared with reductions in the risk of hip and other fractures with initial bisphosphonate treatment. As the authors pointed out, "Among Whites, the number of fractures prevented for each fracture type far outweighed bisphosphonate-associated atypical fractures at all time points. For example, after 3 years, there were 2 bisphosphonate-associated atypical fractures as compared with 149 hip fractures prevented and 541 clinical fractures prevented."[24]

Cannabis use in older adults

Yang et al[25] asked all patients age 65 and older presenting to a geriatrics clinic at the University of California-San Diego during 1 week in 2019 to complete an anonymous survey on personal marijuana use, both tetrahydrocannabinol (THC) and cannabidiol (CBD) products.

They found a 15% rate of use (83 of 568 respondents), with 50 respondents stating that they started as an older adult. Forty-six percent reported CBD use only. The remainder either did not know what they were using, used only THC, or used both THC and CBD. Reasons for use included pain, insomnia, and anxiety. The most common side effect (n = 5) was dizziness. Three people stated that no one knew about their use, and 34 said that their healthcare provider knew.[25]

Maxwell et al[26] report similar trends from the Behavioral Risk Factor Surveillance System in the United States. They advise researchers and clinicians to be more attentive to potential cannabis use in older adults and call for clinical trials to study the effects on this population.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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