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**Review Article**

# Osteoarthritis -Vitamin D Research Observations and Implications for Impacting the Current and Predicted Future Osteoarthritis Global Burden: a 2021-2025 Overview and Commentary

**Ray Marks***

*Department of Research, Osteoarthritis Research Center, Box 5B, Thornhill, ONT L3T 5H3, Canada*

***Corresponding author:** Dr. Ray Marks, OARC Clinical Research and Education Director, Ontario L3T 5H3, Canada

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## Abstract

Osteoarthritis, the most prevalent musculoskeletal disease remains an enormous global source of debility and disability. A disease with multiple progressively degenerating physical manifestations including joint tissue damage, inflammation, bone and muscle pathology, an adequate vitamin D intake may prove helpful, especially in protecting vulnerable older adults from undue pain and suffering and excess joint destruction. Building on a prior in depth overview capturing almost all data on this topic, here we present some current 2024 data on this topic. As a whole, while a vitamin D deficiency is one possible target of paramount importance in ameliorating osteoarthritis pain and cartilage destruction, no firm conclusions currently prevail that could help mitigate the osteoarthritis global burden despite a strong rationale for believing in its potential explanatory and therapeutic attributes.

**Keywords:** Aging; Cartilage; Intervention; Joint Inflammation; Osteoarthritis; Pain; Vitamin D

## Introduction

Osteoarthritis a highly disabling painful joint disease affecting the freely moving joints of at least 528 million persons over age 55 years worldwide has been and remains an immensely costly public health challenge with few means of its mitigation using safe cost-effective approaches despite years of research [1-3]. A commonly progressive disease affecting multiple joint tissues and their biochemistry, structure, and physiology, a role for a viable low-cost amelioration strategy remains elusive, albeit essential, in light of the rapidly increasing aging population and longer life expectancy of the average adult, coupled with earlier and younger osteoarthritis diagnoses. This is because the disease which may begin in early life as well as later life usually progresses and may spread from a single joint to others, commonly inducing substantive incremental bouts of intractable pain, joint inflammation, muscle mass declines, joint stiffness and instability, depression, sleep challenges, and multiple functional limitations that may require increasingly costly health and social support interventions and streamlined timely care [3,4] .

In this regard, an increasing role for non toxic naturally occurring accessible intervention approaches to offset the above challenges and others such as the added impact of comorbid health challenges that do prevail or are anticipated are being sought quite intently. It is also clear that individually delivered multi dimensional applications that may help require a wide array of personnel and/or technology or both may not be available to all, nor proven efficacious, or administered early on in the disease so as to make a key pathogenic impact. Even then, it is probable that the best comprehensive efforts are unlikely to reach the multitudes in need presently and in the future without changes to health care policy and delivery as well as training and life style orientations [4]. Indeed, as is currently the case, it appears osteoarthritis conservative care cannot always be accessed directly-and even if implemented as per a recently recommended comprehensive, sequential, and multimodal plan, this is highly labor intense and requires large time and equipment investments and training and may be unsustainable as well as failing to alleviate osteoarthritis pain in this complex disease, especially if it relies on invasive remedies and omits a focus on basic dietary elements and exercise [3-6]. At the same time, even if resorted to, none of the many pharmacologic approaches that are considered mainstream are found totally safe or disease modifying, and most are not risk free or inexpensive. There is also a need as well for alternatives to narcotics, injections, gene therapy, and surgery to reduce pain [3, 4] and to examine how the present and emergent osteoarthritis burden can be mitigated or averted. This seems to be imperative, because in Indonesia for example, a reasonably advanced country osteoarthritis cases more than doubled from 1990 to 2019, with increases of 153.12% in males and 143.36% in females

and these were higher rates overall than those in China, India, Singapore, as well as the global average, suggesting some role for societal or behavioral factors. Most noteworthy was that younger people had a higher prevalence rate of osteoarthritis growth than older groups, thus negating the widespread aging associated osteoarthritis causative myth. Moreover, global cases of knee osteoarthritis alone are indeed of great salience to address if the disease at this joint alone is projected to increase by 74.9% by 2050, a huge concern given that currently over half of patients reportedly remain dissatisfied with the extent of their pain relief [6].

Studied widely in this regard are the inflammatory disease mechanisms and cellular responses of osteoarthritis along with a possible role for obesity, sedentary lifestyles, and poor nutrition [7, 8]. Alongside these factors vitamin D levels seem especially important to consider. over the long-term because it appears osteoarthritis cartilage degradation starts with an aggrecan loss that may be impacted by vitamin D because this vitamin plays an essential role in abating several inflammation-related processes and can protect the collagen and proteoglycan structural content of cartilage from excess attrition in the case of damaged cartilage [9]. Very key as well are observations that vitamin D insufficiency is a potential predictor of increased mortality risk in the osteoarthritis population [10], but may be protective to some degree when present at optimal physiological levels [11-13].

## Aims

This review aimed to update the extent of support for the idea that vitamin D, an established mediator of bone tissue biology, growth, and development with powerful antioxidant and anti-inflammatory properties may be an influential modifiable factor in the context of efforts to minimize, modulate or mediate osteoarthritis disability and extent. A secondary aim was to establish whether further research appears warranted in this regard given the burden of the disease and the purported role vitamin D plays in many key biological processes, as well as metabolic, genetic, molecular, and neurological processes, implicated in osteoarthritis, an idea disputed by several researchers over the years, but not all.

Tested is whether vitamin D has a distinct bearing or a mediating role in the osteoarthritis pain experience and if its presence can be a determinant of the magnitude of the disease burden.

## Methods

To achieve these abovementioned review aims and one that builds on an extensive 40 year review of available documents housed in PUBMED, PubMed Central, Science Direct and Google Scholar, data from the years 2021-2025 were sought using the key terms Global Burden/Vitamin D and Osteoarthritis.

In this regard, as of October 21, 2024 all available articles were scanned for salience and salience in the context of the osteoarthritis burden, the current topic of interest. An attempt was made to include all modes of epidemiological study, clinical, preclinical experimentation, and intervention strategies, and to thereby establish if a need exists for more osteoarthritis preventive efforts that could basically be made available to large population sectors, but may be underutilized or unrecognized at present. The data bases chosen were assumed to house state of the art and gold standard papers on this topic sufficient for arriving at a reasoned opinion through a narrative lens. Excluded were all data that failed to address the current review issues in some way, studies where vitamin D was co-administered with other compounds, vitamin D and cognitive functions, hypertension, and obesity, plus rheumatoid arthritis and joint surgical studies.

All forms of osteoarthritis were examined collectively given the limited data on forms other than the knee joint. Only English based articles were deemed acceptable. To avoid any confusion in discussing and comparing studies given the prevailing array of diverse vitamin D terminologies in this body of data, among other factors, this review elected to employ the generic term 'vitamin D' to represent any related set of facts. This is not a systematic review, however, and readers can learn more by exploring the current cited reports and specific vitamin D analogues as well as some prior reports [eg., 13-15].

## Key Findings

As among the 469 publications listed on PUBMED as of January 30, 2021 we reviewed previously and that referred to vitamin D and osteoarthritis [15], many current listings failed to focus on this topic in a meaningful way and many were excluded because they were proposals, or conference presentation summaries.

Moreover, as of October 21, 2024, the data examined similarly revealed only a small number of relevant recent studies even when extending the number of data bases. These data were examined whether they were stand alone studies or current reviews and while somewhat favorable as regards the relevance of this topic when considered as standalone studies, do not however appear to support a role for vitamin D in osteoarthritis mitigation to any degree that could drive practice when viewed in systematic reviews. Consequently, even if vitamin D deficits do seem to affect large numbers of osteoarthritis relationships or have a strong bearing in the disease cycle in some severe cases of older sufferers, very few researchers feel reversing the osteoarthritis state through vitamin D assessments and optimization may be possible. However, as in the past, a firm case cannot be made in any manner to date, hence, most researchers call for continued research and efforts to measure and assure vitamin D sufficiency to help protect bone [12] and avoid a severe and rapid destructive form of osteoarthritis progression and disability [14]. As well, even if supplementation appears to have no significant long term osteoarthritis impact [16], several reports continue to show valuable pain relief and other multiple post supplementation benefits.

In addition, a recent report that conducted a meta-analyses of randomized controlled trials on the effects of vitamin D on fracture risk, falls or osteoarthritis, came to the conclusion that 1000 IU daily should be recommend for cases at increased risk of vitamin D deficiency. The group also addressed the identification of patients possibly benefitting from a vitamin D loading dose to achieve early 25-hydroxyvitamin D therapeutic level or from calcifediol administration [17]. In another recent study high rate of vitamin D deficiency were found in association with knee osteoarthritis presence [18]. Due to its anti inflammatory and metabolic bone mediating linkages a role for vitamin D in osteoarthritis care is also suggested to be of value for example, in the context of micro nutrients or neutraceuticals and/or bioactive products and their appropriate usage [19-21]. It is also suggested that vitamin D significantly reduces carti-

lage cell death and alleviates cartilage extracellular matrix degradation, a hallmark of osteoarthritis pathology. In addition, the mechanism underlying vitamin D cell death impacts can be verified and appears to foster the maintenance of cartilage homeostasis [22]. Subject to further study, it is further proposed vitamin D injections may prove beneficial in efforts to foster cartilage repair via this process or others [23].

As well, used in tandem with curcumin-a common spice used in the East, both vitamin D and curcumin used together tended to attenuate the expression of proinflammatory cytokines implicated in osteoarthritis and appears to have the potential to mitigate pathology [24].

Other data show possible genetic influences of vitamin D as far as osteoarthritis development in obese cases is concerned that would be valuable to examine in its own right [25]. In addition, it appears those low vitamin D levels found in knee osteoarthritis, the most common disease form, may be positively correlated with and thus denote an increased risk of the disease [26,27]. Unsurprisingly, even in the absence of robust findings, a call has been made regarding the importance of monitoring and maintaining adequate vitamin D levels with a view to potentially reducing the risk of knee osteoarthritis as well as its burden, particularly in females, older populations, and obese adults. This approach may well guide healthcare providers in the process of tracking the risk status of their clients, and in developing tailored comprehensive approaches to reduce the risk of this condition that may reflect a remediable vitamin D deficit [28].

Another recent analysis showed that among participants who did not report having knee surgery, 2-year vitamin D supplementation and maintaining sufficient vitamin D was linked to modest improvements in knee function and depression scores in those with knee OA compared to placebo [29]. A further meta-analysis tended to affirm a role for vitamin D in the osteoarthritis disease and treatment realm [30]. Furthermore, a recent report showed both calcipotriol – a vitamin D analogue and vitamin D3 or 1,25(OH)2D3 have effects similar to those of glucocorticoids without their apparent toxicity and might hence prove an eligible candidate to the local treatment of arthritis in selected cases [31]. Additionally, vitamin D has been shown to regulate cartilage cell death processes through multiple pathways that may be harnessed as a novel approach for restoring the functionality and survivability of damaged cartilage cells. Other studies supporting the importance of vitamin D, are those that have observed its impact on knee osteoarthritis pain, inflammation, and destructive enzyme levels, plus sarcopenic obesity associated with osteoarthritis [32-34]. Moreover, vitamin D3, through its direct and indirect influence on bones and joints may also play an important role in the development and progression of degenerative joint diseases [35] as well as physical performance, including walking speed [36].

Chen et al. [37] conclude that vitamin D in the form of 1,25(OH)2D3, plays a key role in preventing the onset of aging-related knee osteoarthritis as shown in mouse models of this condition. Moreover, it appears vitamin D supplementation may serve as a novel therapeutic in combating the disease at the knee [38] even if its utility is yet disputed or remains in question [39, 40]. To the contrary early diagnosis and management of any prevailing vitamin D deficiency may provide a window of opportunity that can serve to delay the ongoing degenerative process of knee osteoarthritis even in sunlight rich regions [41]. Moreover, vitamin D supplements can improve subjective pain and function in adults with knee osteoarthritis, despite a lack of strong evidence that vitamin D supplementation can prevent structural progression [42].

Used in conjunction with Gukang capsule-a healer or promoter of fracture recovery vitamin D2 recently appeared to reduce inflammation, improve cartilage metabolism, accelerate knee function recovery, and improve the clinical effect in elderly patients with knee osteoarthritis.

Others in addition imply a favorable role for vitamin D in averting knee osteoarthritis and /or its severity and disease duration [44] and that low vitamin D levels may be found in many cases of knee osteoarthritis that appears correlated with its severity and which is palliated to some degree in some cases of vitamin D supplementation. This may be via its influences on cell signaling pathways involved in cartilage cell degradation and inflammation as well as osteoarthritis clinical signs, such as chronic widespread pain [45,46,47], even if not causally linked [48,49] and any favorable therapeutic effects are non-conclusive [50] and of dubious significance [51], albeit holding great promise [52].

However, it is possible more careful technology assisted study may reveal a role for gene based attributes of key vitamin D receptors as well as various epigenetic aging factors including nutrition and lifestyle factors plus brain based vitamin D impacts that have not been the subject of any intense scrutiny to date in either negative or positive orientated study results [53,58]. However, in the interim, as was observed in 2021 [15]-though available recent clinical studies show some degree of vitamin D deficiency/insufficiency and/or that repletion may serve as a prognostic factor [58], as of mid October 15 2024 these currently reviewed past five-year observations are clearly non uniform or conclusive and need to be updated in more insightful carefully designed and controlled studies. The reliance on systematic reviews to derive practice in the interim must await more robust efforts that employ biomarkers and objective attributes of disease micro and macro functional features, inflammation, and metabolism, and enact strategies that are better standardized and include careful sample selection and uniform vitamin D measures in both observational as well as double blinded randomized controlled studies [60].

Confounding factors at present that may be obscuring study interpretation and should be eliminated as far as possible are:

- Discrepant and/or arbitrary study cohorts, themes and design attributes
- Lack of follow-up periods of substantive duration in prospective studies
- Failure to control for age, body mass, presence, number, and type of chronic conditions
- Unknown medication usage rates, and types of medication usage
- Unknown experimental and control group interventions and supplement usage often assumed or unknown
- Degrees of dietary quality and outdoor sunlight exposure often unknown
- Numbers and types of affected joints/radiographic grade of disease
- Extent of and types of any co-interventions
- Disparate and/or insensitive outcome assessment mea-

sures
- Failure to measure biomechanical and inflammatory disease correlates objectively.
- Possible patient adherence and sample size issues, as well as differences in joint and mobility, alterations in health and mental health status that impact vitamin D, plus the fact that obese cases may need higher doses of supplementation, coupled with the persistent use of subjective measurement approaches, very limited arrays of key disease marker measurements, and arbitrary vitamin D cutoff points

## Discussion

This current 2024 five year brief overview and scan of what we currently know about osteoarthritis and vitamin D linkages was undertaken given the divergent views that prevailed in this regard as of 2020 [see citation 15], and a belief that it has become evident that any form of palliative or reparative treatment among older osteoarthritis sufferers and especially those that can safely reduce pain at low cost and made available to most, would be highly prized. At present however, osteoarthritis cases must depend largely on an array of pharmacologic and/or surgical interventions of varying degrees of efficacy and effectiveness for its amelioration, even if this reactive mode of intervention fails to offer windows of opportunity for risk reduction and cartilage repair. For example, in the realm of preserving muscle mass, cognitive, and strength and averting falls and fractures associated with declines in serum vitamin D in older adults as well as in those with osteoarthritis pathology [18,61-63], and are experiencing inflammation and pain [64], and bone mass declines and impaired bone homeostasis [12,65,66].

Indeed, despite considerable background research on the importance of vitamin D in health maintenance in general, as well as its ability to potentially minimize some degree of osteoarthritis risk and severity when present in the serum at physiological levels, very little definitive consensus has been forthcoming over time in this regard. As a result, it highly probable many older adults are suffering and will suffer excess osteoarthritis pain and its disabling impacts. Moreover, if vitamin D repletion where needed is not forthcoming in a timely way, its impact when administered may have waned, despite several well-founded reasons for anticipating its biological as well as pathophysiological mitigating attributes and remedial properties.

That is, despite a reasonably strong underlying rationale for believing vitamin D is tentatively important for purposes of ensuring optimal joint health at any age, and that older persons with osteoarthritis may be at risk for a reduced ability to take up vitamin D or are less likely to be exposed to its sunlight origins if unable to move freely, their greater need for this vitamin especially those with inflammatory joint changes may go unnoticed or assessed.

Additionally, it remains relatively unknown as to the degree of influence suboptimal vitamin D levels are likely to have as far as being related in some way to the presence of biomechanical and biomarker outcomes of osteoarthritis. A lack of insights in this regard extends to understudied joints or in cases where multiple joints are affected and where changes in the face of vitamin D depletion or repletion or both have rarely been examined other than through a subjective lens of assessment. Details too of what designated categories of vitamin D mean in selected studies, but not others, and that may overlap [65], along with the unknown role of supplementation adherence or excess supplement intake that may go unchecked, and reports based on memory may explain some of the divergent findings to date, as may the widely diverse modes of inquiry, samples, and designs. Thus, even where attempts are made to overcome some of these oversights, as in the past, current data must continue to be largely suggestive, rather than confirmatory or definitive.

This seems unfortunate because several authors have noted a potentially valuable role for considering how vitamin D might mediate or moderate the highly resistant form of pain experienced by people with osteoarthritis, and its impact on function and life quality [43-45], including related bone and cartilage damage. Moreover, multiple studies strongly support the possibility of a vitamin D deficiency and general poor health and frailty in the older population that could impact osteoarthritis risk and progression as well as recovery and treatment responses. Vitamin D also possesses multiple potential capacities for prevention of osteoarthritis progress, including decreases in cell death and the expression of damaging pro inflammatory cytokines, in addition to its well documented key bone building attributes, but while promising, its utility and application must await future careful study.

Indeed, although this current work, which attempts to update prior work has observed the findings of prior work has some salient revelations, the overall topic and its validity remains essentially in question, with few exceptions. That is, very little progress has been made of late, and thus the merits of most of the research conducted for 40+ years has still not resulted in better clinical practices or osteoarthritis outcomes for this progressive disease, rather more are found at a younger age to be vulnerable than anticipated. As a result, the hypothesis that on balance more good than harm can come from supplementing deficient vitamin D in the realm of joint care at any stage or age is not mainstream or accepted practice. Contributing here are possible vitamin D fluctuations due to aging and lifestyle factors and behaviors, poor patient adherence to recommended therapies, differences in joint status and mobility, health and mental health status.

A role for the fact that overweight or frail cases may need higher doses of supplementation, that genetic based vitamin D receptor differences may drive results, plus the persistent use of a limited number of subjective measurement approaches of unknown validity and sensitivity to assess progress or interactions in the face of diverse forms of vitamin D and arbitrary vitamin D cutoff points may be perpetuating the prevailing uncertainty in this sphere.

In particular, careful efforts to clearly define and measure vitamin D adequacy levels for different demographic and age categories and to monitor vitamin D intake or vicarious exposure over time, especially if surgery is indicated, along with efforts to study adequate representative samples with varying degrees of pathology appears warranted. As well, use of validated markers of cartilage pathology and inflammation, biomechanical, radiographic, and functional measures, and whether correcting 'deficient' vitamin D levels yields changes in one or more of these osteoarthritis correlates are indicated.
What the optimum level of vitamin D should be at different

disease stages-what modes of delivery are most likely to yield adequate vitamin D levels, and how often these should be applied clearly also warrants attention. In addition, health conditions that might affect vitamin D absorption, and changes to or reduced function of the vitamin D receptors that regulate vitamin D uptake and signaling should be acknowledged in any future exploration and carefully examined in systematic reviews.

At the same time deleterious vitamin D repletion outcomes and their causes should continue to be sought, and counter-hypotheses generated and tested. Determining how long it would take to impact any aspect of osteoarthritis pathology in the face of insufficient vitamin D, and applying different supplementary doses, over varying time periods, followed by salient outcome tests might be especially helpful in elucidating what is needed or not needed and why.

In the interim, notwithstanding the highly commendable recent attempts to examine vitamin D as a correlate of osteoarthritis, the immense and incalculable global burden attributed to osteoarthritis will not be duly impacted in this regard in our view until further research in this realm can better establish if vitamin D status is a correlate or mediating factor of osteoarthritis outcomes and if so, in what regard. Moreover, since only the knee joint has been studied to any degree, the question of how vitamin D interacts with other forms of osteoarthritis requires study to eliminate misconceptions that could be costly if its potential benefits are overlooked, or harm is caused inadvertently. Crafting more comparable carefully controlled and adequately powered research studies across different laboratories and settings, especially the community setting, and focusing on muscle responses to vitamin D may help immensely to uncover important clinically relevant intervention and prevention implications. Also advocated are more basic research studies that examine the impact of vitamin D on osteoarthritis joint structures other than cartilage, along with trials that examine varying degrees of structural integrity and how the degree of pathology influences the findings, may help clarify the importance of vitamin D across the various stages of the highly debilitating osteoarthritis pain and disability cycle, or explain the reasons for failure as well as successes in supplementation studies.

At the same time, special attention directed towards monitoring the extent of any prevailing biomechanical joint derangements and vitamin D serum levels, plus the role of vitamin D receptor status, injurious daily activities, low vitamin D intake or exposure, and bone health status issues are highly desirable promising important study targets to carefully pursue in the future in our view. Efforts to capture the degree of exposure to sunlight and foods containing vitamin D, adherence to any self-administered vitamin D supplements, and overall health recommendations by study participants in supplementary as well as retrospective analyses are similarly indicated. The possible role of medication or illness interactions and vitamin D status in those with osteoarthritis also warrants more study and assessments via validated biochemical, radiographic, biomechanical instruments and disease markers that are sensitive to change and can be administered in a bias free paradigm [67]. A role for vitamin D in mediating joint instability pain, and poor osteoarthritis outcomes despite possible impacts on cartilage protection and inflamation that is rarely studied is also indicated [68-74].

## Concluding Remarks

Despite decades of research, it is impossible to derive a clear understanding of whether or how deficient vitamin D serum levels are indeed associated with pain provoking inflammation that often accompanies osteoarthritis, or whether vitamin D is a possible causative and/or protective agent worthy of consideration as recently discussed and observed [68-76].

In addition, it is acknowledged such data may yet exist, but may have been omitted inadvertently, however, after surveying more than 100 related papers in 2020 and another 65 since then in this report, wherein most were located in the world's leading data base of PUBMED-deemed reliable and peer reviewed- it appears safe to propose that even if persistent vitamin D deficits appear to have the potential to accelerate or magnify any prevailing joint pain found in most older adults suffering from osteoarthritis, this viewpoint is not held by all.

It may be possible however to conclude that an individual struggling with painful osteoarthritis who is under stress is particularly vulnerable to more distress and damage than not, and may not be able to secure sunlight or food based vitamin D exposure even if they have an increasing need for vitamin D to minimize their prevailing health challenges that can provoke injury and inflammation in its own right. When multiplied by almost 600 million possible cases over time, the costs of failing to take the time to screen for vitamin D levels in vulnerable adults are likely to exceed all current estimates and projections in multiple ways.

In the meantime, we conclude timely research to generate more insight into how vitamin D may be an important osteoarthritis pathogenic correlate will permit more robust and adequate translation of prevailing data showing considerable promise at all disease stages and in most osteoarthritis joint disturbances to the clinic. In particular, research attempts designed to differentiate the association of vitamin D levels among distinctive osteoarthritis sub-groups with and without verifiable oxidative damage as well as its possible association with disease severity age and disease prognosis may prove especially insightful. After that, meticulously and rigorously designed bliended studies to rule out competing hypotheses, and to avoid undesirable cross-sectional inferences that do not take into account the fact that reported vitamin D intake on a food survey delivered retrospectively may not be the same as actual time-based plasma levels are indicated. Since its effects may be joint specific, as well as dose-dependent and take weeks or months to unfold and be influenced by gender among other factors such as age, health and disease status it appears much study in this regard is imperative.

However, until more is known, we further conclude it is not possible to support investments in this regard as far as both screening and intervention are concerned. On the other hand, careful analyses and prescriptions may well show favorable cartilage repair and protective processes, bone maintenance, tendon healing, collagen production, stress reduction, neural regeneration, muscle atrophy prevention, plus inflammation control. Indeed, when carefully screened for and duly titrated and applied as indicated, vitamin D supplements or exposure may yet help to 1) enhance overall wellbeing and independence, 2) offer a low cost widely available safe option for physically, and economically vulnerable older adults, 3) reduce cases of older adult with osteoarthritis from requiring placements, narcotics, or daily services, 4) foster more rapid and overall surgical re-

covery rates and results, 5) engender fewer overall demands on health providers amidst shrinking resources and budgets, 6) reduce the global burden of osteoarthritis while enhancing the ability of many elders to age 'in place'.

Moreover, efforts to close the gaps in the literature are likely to have multiple life affirming, independence and cost related implications for many, including excess surgical costs and need.

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