



The Potential for Prevention Science in Middle and Late Adulthood: a Commentary on the Special Issue of Prevention Science

Marina Epstein¹ · Rick Kosterman¹ · Richard F. Catalano¹

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Abstract

This commentary on the special issue of *Prevention Science*, “Toward a Lifespan Prevention Science: A Focus on Middle and Late Adulthood” reviews the studies included in the issue, compares findings, and makes recommendations for future directions in this emerging field. Articles in this issue addressed a number of the key elements of prevention science, including identifying proximal and distal risk and protective factors that play a role in middle and late adult health and well-being, providing preliminary evidence for a preventive intervention to moderate stress reactivity, and proposing a theoretical approach to preventing substance misuse across the lifespan. Our commentary centers around three critical areas for mid and later life prevention science: the importance of theory building, a focus on alcohol and its role in midlife health, and health disparities. Each of the articles in this issue touched on at least one of these areas. We conclude that a focus on prevention in mid and later life has strong potential, and further research is needed.

Keywords Midlife · Late adulthood · Preventive interventions · Substance use · Health disparities

This special issue of *Prevention Science* seeks to identify the unique needs of individuals in middle and late adulthood in order to develop effective preventive interventions for this period of development. The collected manuscripts provide diverse ways of addressing this call, including papers that document developmental epidemiology of the course of substance use and adversity across the decades leading into middle and late adulthood (e.g., Green; Patrick; Bourassa), identify precursors of a variety of problems and address unique stressors during mid and later life (Bolkan et al., 2023; Lee et al., 2023; Luo et al., 2023; Stawski et al., 2023; Turner et al., 2023; Vipperman et al., 2023), develop theories applicable to enhanced well-being (Bolkan et al., 2023; Dykstra et al., 2023; Luo et al., 2023; Vipperman et al., 2023), and directly test interventions (Castro et al., 2023). Together, these studies cover a broad landscape of mid and later life health, including considerations of mental health, substance use, cognitive decline, and caretaking. These studies also directly address health disparities by race, gender, geographic location, and socioeconomic status.

Midlife has traditionally been defined as roughly ages 40 to 60, but longer lifespans have meant more healthy years devoted to the roles and life events that characterize this period (e.g., children reaching adulthood, career development) (Infurna et al., 2020). Understanding midlife and later adult health problems and disparities is particularly important for those now in their 40 s and 50 s—often labeled Generation X—who are much more diverse both demographically and in timing and structure of family formation than prior generations (Lyons et al., 2015; Pew Research Center, 2019b; Taylor & Gao, 2014). For example, compared with Baby Boomers (currently in their 60 s and 70 s), today’s midlife adults are less White (39% non-White vs. 28% among Boomers) and have more post-high school education (57% vs. 45%) (Bialik & Fry, 2019; Fry et al., 2018). Also, most Baby Boomers entered midlife married with teenage or young adult children, moving toward the “empty nest” stage (Newton et al., 2014; Parker & Patten, 2013), and many were at the peak of their work careers (especially men) with an eye toward retirement or were contemplating a return to work after having raised children (particularly women) (Pew Research Center, 2019a; U.S. Trust, 2017). In contrast, Generation X is more likely to be divorced or not partnered, to have toddlers or no children, and, due to increased participation in postsecondary education, to have greater variability in career stage by midlife (Lyons et al., 2015; Pew Research Center, 2017, 2019b). Generation X

✉ Marina Epstein
marinaep@uw.edu

¹ Social Development Research Group, School of Social Work, University of Washington, 9725 3rd Avenue NE, Ste. 401, Seattle, WA 98115, USA

women are especially more likely to be employed and have both work and parenting responsibilities (Hochschild & Machung, 2012). Research suggests important implications of these sociodemographic differences for health, such as significant links between being partnered and better mental and physical health, and between inconsistent employment and worse midlife health (Carr & Springer, 2010; Lacey et al., 2016).

Little research has focused on Generation X as they enter midlife, making it important to better understand the distal and proximal precursors that influence the later life health and behavioral outcomes of this generation, such as childhood poverty, life-long patterns of substance use, educational performance and attainment, and racial and ethnic discrimination experienced over the life course. These distal and proximal precursors may illuminate promising targets for preventive interventions to improve midlife outcomes. For example, Bolkan et al. (2023) suggested that, “A better understanding of later life adult development may counter ageism and lead to more supportive age-friendly policies and programs that benefit people of all ages throughout the life course” (p. XXX). The compendium of studies in this issue provides a broad introduction to the knowledge development necessary for intervention testing to prevent midlife problems and promote healthy development.

Risk and Protective Factors in Middle and Late Adulthood: A Summary of the Current Issue

Over the past four decades, prevention science has emerged as a discipline built on the integration of life course development research, community epidemiology, and preventive intervention trials (Kellam et al., 1999). A key foundation of prevention science is the identification of risk and protective factors (Catalano et al., 2012) which drive mental and physical health, as well as behavioral outcomes. Extensive reviews of how risk and protective factors affect behavior at earlier life periods have been compiled. For example, prior work by Hawkins et al. (1992) and Stone et al. (2012) reviewed risk and protective factors for substance use during adolescence and emerging adulthood, respectively; DiClemente et al. (2006) documented family influences on adolescent sexual behavior; Farrington et al. (2017) addressed predictors of violence, offending, and delinquency; and Saunders et al. (2014) reviewed risk and protective factors related to child obesity. These risk and protective factors occur in various domains: the individual (e.g., gender, impulsivity, personality traits, history of abuse), family (e.g., harsh parenting, parental substance use, close family bonds), peer (e.g., peer substance use, peers who engage in delinquent behavior, close prosocial friends), school/work (e.g., positive engagement with teachers/school, school dropout, coworker bonding), and larger

neighborhood and societal domains (e.g., neighborhood safety, state and local laws and regulations).

These reviews of bodies of empirical research point to malleable prevention targets and have helped develop and shape effective prevention programs that incorporate the most impactful risk and protective factors for specific developmental periods. Less is known about distal and proximal predictors of midlife behavior and health outcomes and how individual, social, and environmental influences across development contribute to these outcomes. Critical to preventing negative midlife outcomes and promoting positive midlife outcomes is the identification of predictors of these outcomes and when during development they become salient and can be addressed. Once the identification of reliable predictors is established, theory can assist in understanding possible causal mechanisms among the predictors (Catalano & Hawkins, 1996).

A number of articles in this special issue have contributed to this growing research base. Bourassa et al. (2023), Green et al. (2023), Luo et al. (2023), and Stawski et al. (2023) have linked earlier life experiences to midlife and later health and well-being outcomes. Bourassa and colleagues found that early adverse childhood experiences (ACEs) predicted a set of stressors in the 30 s, including stressful life events, perceived stress, negative emotionality, and poor health behaviors (smoking, low physical activity, unhealthy diet, and heavy alcohol consumption). The effect of ACEs was fully mediated by these stressors and health behaviors in predicting broad health outcomes at age 45. These findings provide two potential foci of preventive intervention: early in childhood to reduce abuse and family dysfunction, and in the 30 s to reduce stress, negative emotionality, and increase positive health behaviors. Importantly, Green and colleagues found that early family poverty predicted midlife mortality (by age 58), even if poverty did not persist into adulthood; however, those who experienced early and adult poverty had the highest mortality rates. These results illustrate both the cumulative “compounding impact” of socioeconomic disadvantage and the enduring effects of early poverty on health even if the poverty itself does not persist. Green et al. also showed, however, that educational attainment and, especially, integration in multiple social roles during midlife were protective against early mortality, providing promising direction for preventive intervention for this group. They emphasized that efforts to reduce poverty and increase protection at multiple points over the life course—even in midlife—are potential targets to prevent premature mortality. Early life experiences were addressed by Luo and colleagues who, in a review of studies of life stress predicting later dementia, found that stress and stress responses (e.g., PTSD) in childhood and later in life increased the likelihood of having dementia. Stawski and colleagues examined daily stress processes as predictors

of depressive disorder 10 years later. They found stressor exposure, negative affect, and affective reactivity all predicted later depressive disorder measured in midlife. Thus, conducting preventive interventions to reduce stressors and reaction to stressors during midlife might be a promising approach to reduce later depression.

Other studies in this issue addressed additional concerns of mid and later life, including worsening mental health and substance use problems in recent midlife cohorts, trouble connecting with others, physical and mental declines, concerns brought about by caregiving for both children and parents (i.e., the “sandwich generation”), and the larger effects on quality of life brought by locality and neighborhood contexts. Castro et al. (2023) conducted an experimental trial of a skills training intervention during midlife to improve emotional regulation. They found that the intervention had short-term effects on decreasing negative affect, less diminishment of positive affect on stressor days, and less negative affect on days without uplifts, thus buttressing the findings of Stawski et al. (2023) regarding stress processes predicting depression. It will be of interest for Castro and colleagues to follow those in their study to see if the impact of their intervention extends to preventing later depression. Turner et al. (2023) showed that a discrepancy between age and a (younger) desired age can lead to negative health and mental health outcomes, whereas acceptance of one’s age can lead to more life satisfaction, though it is unclear whether these findings might be bi-directional. The findings of Patrick et al. (2023) fit with those of Green et al. (2023) to underscore the need for social connection as an important protective factor during midlife. Patrick et al. found that non-problematic alcohol use (i.e., not binge drinking) had a protective effect on depression and hypothesized that this was a byproduct of social drinking and therefore a marker of more social connections. The authors offered a possible explanation that depressive symptoms may lead to less socializing and few opportunities for social drinking. A theoretical offering by Rodriguez et al. (2023) proposed combatting decline in cognitive and functional abilities through learning new skills. Interventions based on this work, if designed and implemented, could possibly alleviate the effects of stress on dementia discussed by Luo et al. (2023). Finally, studies by Bolkan et al. (2023) and Vipperman et al. (2023) both focused on aspects of elder caregiving.

Bolkan et al. (2023) provided a comprehensive review of the multiple levels at which elder mistreatment may occur that may guide the prevention of elder mistreatment, such as redefining late adulthood away from a period of decline, providing legislative and community support for community elder centers and support groups, and creating opportunities for greater bonding and connection with others. Vipperman et al. (2023), in turn, identified barriers to service use among caregivers of those with dementia living in rural Appalachia,

stressing the need for more support in navigating the systems of services, financial barriers, and caregiver overload. With Generation X midlife adults being more likely to experience “sandwich generation” stresses than previous cohorts, caregiver burnout—particularly among women—is an increasingly important issue to address.

Finally, theory is needed to understand how the risk and protective factors identified in this issue interact to influence outcomes. Given multiple empirically identified predictors and the multiple possible relationships among them, modeling mechanisms must proceed theoretically to identify the most plausible functional causal associations among them (Bursik & Grasmick, 1996). The goal of any theory of middle and late adulthood behavior and health outcomes should be to explain and predict the onset, escalation, maintenance, de-escalation, and cessation or desistance from these health behaviors and outcomes. Dykstra et al. (2023) provide an example of theory to address proximal predictors of problem drinking that has implications for preventive, harm reduction, and treatment interventions. An advantage of the theory is its flexibility in respect to developmental period, although this flexibility limits its precision when it comes to the unique considerations of each specific age group. As more predictors are identified, broader theoretical perspectives that organize key mechanisms from both proximal and distal precursors will be needed. We have used theory to both understand how predictors interact to produce outcomes and to guide intervention development at multiple developmental stages. A description of these efforts is presented by Cambron et al. (2019). Similar efforts could be made to extend such theories or to develop new theories as more predictors are identified for middle and later life behavior and health outcomes.

Importance of Studying Alcohol Use and Misuse for Middle and Late Adulthood Health

Alcohol is the most commonly used substance, and alcohol misuse is one of the most common health risk behaviors (Substance Abuse & Mental Health Services Administration, 2019). It is associated with poor social functioning and comorbid health problems, and underlies many middle and later life health concerns, including other drug abuse, mood disorders and suicide, serious injury, cancers, heart disease, and respiratory conditions (Lai et al., 2015; National Institute on Alcohol Abuse & Alcoholism, 2019; Room et al., 2005). Alcohol misuse is a significant contributor to accelerated aging and to early disability and mortality among recent midlife cohorts (Case & Deaton, 2015; National Institute on Alcohol Abuse & Alcoholism, 2019; O’Neill et al., 2017). Moreover, there is evidence for particularly large increases in recent decades in high-risk drinking and alcohol use

disorder for those in midlife, with the COVID-19 pandemic exacerbating these increases (Barbosa et al., 2021; Daly & Robinson, 2021; Grucza et al., 2018; Murthy & Narasimha, 2021). Alcohol use is likely to both affect and be affected by key middle and late adulthood contextual factors such as partner/family or employment status and transitions, which in turn impact health. For example, alcohol misuse could hasten diminished family involvement as children age and become more independent; adjusting to a new “empty nest” could bring about increased alcohol misuse.

Of the articles in this issue that considered substance use, the study by Patrick et al. (2023) is most informative because it examined associations between substance use and depression over a 20-year period, between ages 35 and 55. The authors did not find a consistent association between depression and non-problematic drinking in the 30 s, but observed that non-problematic alcohol use was actually a protective factor in the 40 s and 50 s. They also found that binge drinking, cigarette use, and cannabis use were associated with more depressive symptoms. Lee et al. (2023) examined whether health-related problems at different developmental periods might drive a reduction in alcohol use and found confirmation of this hypothesis during midlife and later adulthood (but not before age 45). This was particularly true for those adults who did not report prior alcohol use disorder. Analyses by Bourassa et al. (2023) also found a possible role of alcohol use as a mechanism linking ACEs with poor midlife health. Though heavy alcohol consumption was just one of four indicators used to measure of unhealthy behavior (with smoking, low physical activity, and unhealthy diet), this measure evidenced the strongest indirect effect. In their sample of urban Black Americans, Green et al. (2023) reported that 11.4% of deaths among those age 50 to 58 were alcohol and drug related. They noted that social integration and educational attainment were found to be protective against substance use disorders, suggesting specific avenues for prevention (Green et al., 2010). The possible benefit of social integration echoes Patrick et al.’s (2023) finding that non-binge (possibly social) drinking had an association with *less* depression. Thus, the importance of social engagement may be a key consideration for a thorough understanding of the role of alcohol use in midlife. Patrick and colleagues’ results reinforce the need for interventions to prevent substance misuse and depressive symptoms in midlife, but that also recognize the interplay of healthy social engagement with moderate alcohol use.

Beyond the studies in this issue, effective models of alcohol and drug prevention often focus on youth and young adults, which is a significant limitation of existing research (Dykstra et al., 2023). Yet problematic substance use occurs across the lifespan, and recent data indicate that alcohol use is increasing fastest among those age 50 and older (National Institute on Drug Abuse, 2020). To address this gap, Dykstra

et al. provide an intervention approach based on the lifestyle risk reduction model that is applicable across the lifespan. This model stresses the interaction of behavioral choices with individuals’ biological factors, including age, that increase or reduce the risk of addiction. By addressing factors that facilitate low-risk choices, including social network selection, they found that an intervention based on the model had promising effects on individuals’ perceived risk accuracy and reduced impaired driving recidivism. The authors provide an example of theory application and intervention testing to develop a lifespan prevention approach to substance misuse. It is noteworthy, furthermore, that Patrick et al. (2023), Green et al. (2023), and Dykstra et al. (2023) each point to social factors (opportunities, integration, networks) as important considerations in midlife substance misuse prevention. This is consistent with our view that it is essential to understand the social context of risk behaviors and to identify the social developmental domains (e.g., family, peer, work, community) and processes (e.g., opportunities, skills, reinforcement, bonding) where modifiable precursors can be effectively targeted with preventive interventions.

Another significant limitation of existing research in this area, particularly from a prevention perspective, is that there has been little recognition of how individuals arrive at middle and late adulthood with different histories of alcohol use, including age of onset, severity, and chronicity of use, misuse, and disorder across development. While some studies have included retrospective reports of alcohol use, there is a dearth of research examining how patterns of use and misuse over a person’s life may help explain who develops problems with health and functioning, and the kinds of problems, into middle and late adulthood (Berg et al., 2013; Jacob et al., 2009; Jester et al., 2016). For example, little is known about the midlife health implications of the timing of onset and periods of misuse or the emergence of alcohol use disorder at different developmental stages. To close this gap, there remains a significant need for prospective longitudinal studies that can link developmental alcohol use trajectories with later life health and functioning.

Understanding Health Disparities at Middle and Late Adulthood

As noted earlier, the current cohorts of midlife adults—known as Generation X—differ significantly from the Baby Boomer generation. They have taken significantly more diverse life paths, which drive health disparities. Several papers in this special issue point to the importance of understanding health disparities for a lifespan prevention science. This priority is reflected in the National Institute on Aging Strategic Directions and Health Disparities Framework (National Institute on Aging, 2020, 2023) and amplified by the COVID-19

pandemic (Bambra et al., 2020; Yang & Qi, 2022). In their analysis focusing on ACEs and midlife health, Bourassa et al. (2023) stressed that ACEs are more prevalent in minority and disadvantaged populations and may be an important contributor to health disparities. In a systematic review, Luo et al. (2023) also found that ACEs—which are elevated among minoritized groups—were one of the strongest predictors of later life dementia. Relatedly, in a compelling analysis of disadvantage over the life course and mortality among Black Americans in midlife, Green et al. (2023) showed that childhood poverty increased the risk of early mortality decades later over and above poverty at other points in the life cycle. Viperman et al. (2023) highlighted rurality and location as important aspects of health disparities with prevention implications, elucidating the unique barriers to service utilization in rural Appalachia among family members caring for older adults living with dementia.

An interesting perspective provided by Turner et al. (2023) posits that ageism is itself a dimension of health disparity that is perpetuated at individual, social, and societal levels. They showed that the desire to be younger (often conveyed through ageist attitudes in the media and society in general) can activate consistent daily negative affect that is linked to poorer health outcomes. This desire tended to be higher among men and those with less education. Bolkan et al. (2023) also stressed that ageism is pervasive, intersects with race/ethnicity and SES, and is a major contributor to elder mistreatment. Bolkan et al. noted, however, that ageist attitudes are modifiable, and should be included in discussions of diversity, equity, and inclusion taking place widely in businesses and organizations, as well as through education of younger cohorts and encouraging closer intergenerational interactions. Castro et al. (2023) and Rodriguez et al. (2023) also both provided important perspectives on how interventions could be used to reduce health disparities.

Taken together, the papers in this issue strongly encourage consideration of multiple sociodemographic statuses that are associated with quite different behavior and health outcomes in midlife and late adulthood. Potential disparities by gender, race/ethnicity, and socioeconomic status (including education and employment) should be prominent factors in analyses of later life behavior and health outcomes. Additionally, possible disparities by partner and family status (married, divorced, children in the home, etc.) may be particularly relevant in middle and late adulthood for Generation X given their differences from prior generations. Possible family formations are increasingly diverse, and this has important implications for health (Roberto & Blieszner, 2015; Simon & Caputo, 2018). Interactions among factors driving health disparities are also important to investigate. For example, one finding reported by Green et al. (2023) was moderation by childhood poverty of the protective effect of educational

attainment against premature mortality (no significant effect among those who had been poor in childhood). Findings such as this are a reminder of the complex ways by which the precursors of health in later life may be moderated or mediated, and this can have important implications for preventive interventions. Moreover, many health disparities increase in mid and later life (Infurna et al., 2020), and analyses will benefit from a life course perspective that accounts for processes over time. A comprehensive analysis is needed to understand the breadth and depth of disparities that exist across multiple indicators of later adult health, as well as developmental processes and possible interactions.

The prominent work of Case and Deaton on “deaths of despair” documents an ongoing public health crisis that also underscores serious midlife health disparities (Case & Deaton, 2015, 2017, 2020). They detailed rising rates of mental health problems, physical dysfunction, chronic pain, and mortality among national samples of midlife Americans. These changes have coincided with increases in social isolation, heavy drinking and drug use, reduced rates of marriage, and, for males, reduced labor force participation. But the increases in early mortality have not been borne by all equally. Case and Deaton (2022) stressed that life expectancy among Black Americans has been lower than among White Americans as far back as data have been collected, and this continues to be the case. This gap had been narrowing until around 2010 when deaths of despair, linked to increased opioid use and cardiovascular disease, in the Black and Hispanic communities began to widen the gap again. Yet, Case and Deaton found that education is an increasingly important driver of health disparities. They showed that all-cause mortality in the USA is *diverging*, such that rates are rising for those without a college degree and falling for those with a degree (Case & Deaton, 2022). This was starkly noticeable during the COVID-19 pandemic when those from underprivileged communities (e.g., Black, Hispanic, and Native Americans) and those without a college degree died at higher rates. We think this should be a clarion call to researchers and practitioners that, in addition to race/ethnicity, lack of a college degree may be an ever-growing risk factor for shorter life expectancy. Although post-secondary education is becoming more normative, the *majority* of American adults remain without a college degree, and as Case and Deaton emphasize, this has become “a matter of life and death.”

Conclusion

This special issue is an important advance in the exploration of risk and protective factors relevant in midlife and their role in healthy aging. The collection of work

presented here examines multiple predictors for several midlife outcomes. Also, predictors across developmental periods were considered, providing evidence of both distal and proximal intervention targets. While these studies examined diverse outcomes—composite midlife health, depression, dementia, and mortality—there is clearly a long way to go, and predictors of other middle and late adulthood outcomes need to be studied as well. These include the physical and psychological effects of the COVID-19 pandemic on this population, especially the effects of extreme familial isolation (or increased family togetherness when multiple generations moved closer during the pandemic). In general, as more and more midlife adults become caretakers of their own parents—while often caring for their own children as well—the physical, financial, and psychological burden of these converging responsibilities, especially for women, needs to be examined. In addition, the effects of neighborhood-level and built environment factors, including neighborhood safety, walkability, and proximity to outlets that sell alcohol, nicotine products, or (in some states) cannabis, all remain to be explored.

From the studies presented in this issue, early adversity, education, social connections, and substance misuse emerged as among the most impactful predictors. But the studies also showed that different populations often have different needs. As Green et al. (2023) noted, a sole focus on attainment of higher education may not be helpful for urban Black Americans who were poor in childhood (a subsample they examined), who may benefit more from a direct focus on social integration (e.g., marriage, family, employment). Alternatively, a preventive intervention such as the child tax credit may lift some families out of early poverty (National Academies of Sciences, 2019). Vipperman et al. (2023) showed that rurality can introduce unique health disparities that need to be addressed, suggesting that local population epidemiology be considered when planning preventive intervention, a tenet of prevention science.

A next step to advance this field is to organize the risk and protective factors from these and similar studies into testable theories that can guide the development of interventions. Prevention at all levels is needed, and better understanding of and conceptualizing the unique and continuing challenges adults face in middle and late adulthood are necessary to develop and deliver effective preventive interventions, as well as to launch interventions to curb ongoing high-risk behavior via harm reduction strategies. The Dykstra et al.'s (2023) risk reduction model is one such endeavor, but more work is needed. Interventions for this period of life are rare; the Castro et al.'s (2023) study did show promising short-term effects, but

longer follow-up is crucial for sustained impact. By contrast, interventions for younger cohorts (children, adolescents, and even young adults) are quite common. What is less known is the extent to which upstream prevention has long-term payoffs into middle and late adulthood. Only a handful of studies have followed intervention cohorts beyond adolescence. In one example, work from the Seattle Social Development Project testing the Raising Healthy Children preventive intervention demonstrated effects through the 30 s on better health maintenance behavior, mental health, and other indicators of adult well-being—effects that were significant decades after the intervention in elementary school ended (Kosterman et al., 2019). In another example, participants in the Perry Preschool intervention reported greater employment and less drug use at age 40 compared to a group that did not receive the intervention (Schweinhart et al., 2004), again showing positive effects decades after a childhood intervention. More investigation into the potential effects of childhood and adolescent preventive interventions into midlife is needed, as early interventions that prevent problem behavior and other risk factors for midlife health are likely to have greater cost–benefit payoffs than interventions in adulthood that are often more treatment oriented after problems have onset.

Continuing to improve our understanding of health disparities in middle and late adulthood remains key to promoting a healthy generation of midlife and older adults across an increasingly diverse population. Testing of new and existing interventions should ensure that they are at least equally effective for different racial/ethnic, gender, and socioeconomic groups. Notably, where health disparities exist, it is unclear whether simply establishing equality in effectiveness will move the needle on reducing such disparities (Frohlich & Potvin, 2008). Universal approaches may need to be retooled to ensure robust effects for marginalized groups or, alternatively, indicated or selected interventions may be needed. Further, as midlife adults move into older adulthood, it is important to consider how interventions administered at midlife will affect longer term outcomes. For example, while it may not be possible to reverse dementia after onset, Rodriguez et al. (2023) provided an approach for possibly slowing down the disease. Similarly, it may not be too late to reduce the adverse health effects of substance misuse if midlife adults cut down (e.g., decrease alcohol use) or switched modes of use (e.g., replace cigarettes with electronic nicotine delivery systems or e-cigarettes, which are safer for lung health (National Academies of Sciences, 2018)). Encouragingly, the papers in this issue help to advance the tenet that a lifespan prevention science should hold consideration of health disparities at its core, as well as consider harm reduction approaches for existing problems.

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Declarations

Ethical Approval All research protocols involving human participants were approved by the University of Washington Institutional Review Board and were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments.

Informed Consent Informed consent was obtained from all study participants.

Conflict of Interest The authors declare no competing interest.

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