New and Future Directions in Integrative Medicine Research Methods with a Focus on Aging Populations: A Review

Lindsey M. Knowles\textsuperscript{a} Perry Skeath\textsuperscript{a} Min Jia\textsuperscript{a} Bijan Najafi\textsuperscript{b} Julian Thayer\textsuperscript{c} Esther M. Sternberg\textsuperscript{a}

\textsuperscript{a} Arizona Center for Integrative Medicine, Institute on Place and Wellbeing, Department of Psychology, and 
\textsuperscript{b} Interdisciplinary Consortium on Advanced Motion Performance (iCAMP), Southern Arizona Limb Salvage Alliance (SALSA), University of Arizona, College of Medicine, Tucson, Ariz., and \textsuperscript{c} The Ohio State University, Columbus, Ohio, USA

Key Words
Integrative medicine · Aging populations · Stress response · Heart rate variability · Sweat biomarkers

Abstract
This review discusses existing and developing state-of-the-art noninvasive methods for quantifying the effects of integrative medicine (IM) in aging populations. The medical conditions of elderly patients are often more complex than those of younger adults, making the multifaceted approach of IM particularly suitable for aging populations. However, because IM interventions are multidimensional, it has been difficult to examine their effectiveness and mechanisms of action. Optimal assessment of IM intervention effects in the elderly should include a multifaceted approach, utilizing advanced analytic methods to integrate psychological, behavioral, physiological, and biomolecular measures of a patient’s response to IM treatment. Research is presented describing methods for collecting and analyzing psychological data; wearable unobtrusive devices for monitoring heart rate variability, activity and other behavioral responses in real time; immunochemical methods for noninvasive molecular biomarker analysis, and considerations and analytical approaches for the integration of these measures. The combination of methods and devices presented in this review will provide new approaches for evaluating the effects of IM interventions in real-life ambulatory settings of older adults, and will extend the concept of mobile health to the domains of IM and healthy aging.

Introduction

The global population of adults aged 65 years and older is projected to grow from an estimated 524 million in 2010 to 1.5 billion by 2050 [1]. Older adults’ medical conditions are often complex, with approximately 70% of Americans suffering from one or more chronic medical conditions [2]. Polypharmacy, greater neuropsychiatric sensitivity to medications’ side effects, altered pharmacokinetics (e.g. absorption and drug metabolism) and pharmacodynamics (the physiologic effects of the drug), and irregular compliance present important considerations for the health care of older adults. Integrative medicine (IM) coordinates prevention and treatment across multiple health issues, making it particularly well suited for aging adults’ complex medical needs.
IM is a healing-oriented practice that combines conventional and complementary methods to take account of the whole person (body, mind, and spirit) and all aspects of lifestyle [3]. Integrative approaches to health, which include diet, exercise, and mind-body techniques for stress reduction [3, 4], are thought to enhance disease prevention and to prevent, slow or even reverse some aging processes [5]. The current generation of aging adults, more than any previously, seeks to engage in these health-promoting activities [6–9]. Of concern, a study of over 3,000 ambulatory older adults in the US found that almost three quarters used at least one prescription drug and one dietary supplement, and research has shown that certain prescription and supplement combinations can lead to adverse effects [10]. Therefore, greater awareness of older adults’ increased utilization of IM components and interventions is necessary. Moreover, it is important to adequately document health effects of IM approaches for disease treatment and prevention, particularly in aging populations who stand to benefit from IM’s holistic approach.

At the same time, such documentation presents challenges. Although some studies using a typical randomized clinical trial approach show benefits of IM intervention components for specific conditions in elderly populations [11, 12], there remains a paucity of evidence for the impact of IM interventions in the elderly [13]. This may be in part because IM treatment plans operate in the context of holistic patient care and are often more complex and interactive than treatment plans in conventional medicine [3, 4].

To meet these challenges, new experimental approaches are needed. Ongoing advances in methods and technologies can strengthen experimental research in IM as applied to older adults who may benefit most from IM’s holistic approach. This review focuses on sensitive, noninvasive methods to measure psychological, physiological, behavioral, neuroendocrine, and immune/inflammatory responses, coupled with an advanced analytic approach to merge these measures.

**Multivariable Assessment from Psychological to Molecular Measures**

IM practices are highly competent in conventional, complementary, and behavioral domains. Often, all three of these domains are prominent in IM interventions, and the specific elements of these domains are selected, individualized, and organized by the IM provider and patient to interact synergistically [3, 4]. In elderly populations, low-risk solutions as a first-line approach to common problems (e.g. pain) are especially important due to the more prominent risks of polypharmacy, altered metabolism and absorption of medications, and increased neuropsychiatric sensitivity to medications [14]. IM approaches to health issues like pain management include a combination of conventional Western medicine and massage, acupuncture, meditation, and herbal supplements. The IM provider considers the elderly patient’s interests, comorbidities, current medications, and physical health to create an individualized treatment plan. The patient may respond with improved quality of life, improved mood, reduced stress response, improved activity, and/or reduced inflammation, as well as with reduced symptoms or disease activity. Because the patient may respond in only one or a subset of domains, a comprehensive assessment of psychological, behavioral, physiological, and biomolecular domains is important in determining the effectiveness of IM interventions.

**Qualitative and Quantitative Methods in Psychological Research**

Psychological responses can be collected as qualitative or quantitative data. Qualitative data are typically gathered through semi-structured interviews consisting of open-ended questions. Quantitative data typically involve participants completing validated scales that assess certain construct(s) in a multiple choice format, which permits statistical analysis. Importantly, psychological data can substantially aid in the evaluation of patient responses to treatment and can be sampled in real-time using smartphone technology [15].

Qualitative data analysis can lead to new approaches to treatment. In particular, the grounded theory qualitative approach is a complex iterative process by which researchers identify the content, underlying processes, and characteristics of a construct of interest [16]. For example, in a study of psychosocial and spiritual ‘life-transforming change’ (LTC) among cancer survivors, Skeath et al. [16] found that the construct that best matched the LTC process was experiential learning. This construct had seldom been applied in medical research, including previous studies of cancer survivors, yet it provided a much better description and understanding of LTC than more obvious constructs, such as coping and posttraumatic growth. Skeath et al. [16] argue that supportive care teams and oncology-related specialists could help facilitate LTC in cancer patients by supporting the experiential
learning process. Thus, the grounded theory qualitative approach provides a set of strategies for conducting rigorous and novel qualitative research that can be translated in health care settings.

In addition to qualitative data, the use of validated questionnaires and scales yields numerical quantitative data that can be analyzed through statistical inference. Approximately half of all American adults and 31% of those aged 55–64 years own a smartphone, and advances in smartphone technology and its increasing use in research allow for the collection of quantitative and qualitative data in real time [17]. Specifically, the experience sampling method (ESM), also referred to as ecological momentary assessment (EMA), sends participants questions to answer at specific time points throughout the day for the purpose of sampling their experience in real time [18, 19]. Consequently, ESM/EMA considers variation in measured variables over time, both within and between individuals, and minimizes retrospective bias. For example, Murphy et al. [20] used EMA, rather than traditional retrospective self-report methods, in a study of 60 older women with hip or knee osteoarthritis to assess their experience of pain and fatigue within their daily routine. They found that higher momentary fatigue was associated with lower physical activity levels, and contrary to the study hypotheses and prior research, higher momentary pain predicted higher levels of physical activity. Therefore, Murphy et al. [20] argue that interventions to increase physical activity in this population should broaden the traditional focus on pain management to include management of fatigue. There are many options for establishing sampling intervals in ESM/EMA, including sending questions at predetermined time intervals or randomly throughout the day, or questions that can be triggered by certain events, such as after a doctor’s appointment [18]. A combination of sampling methods may be used depending on the purpose of the study and the nature of the construct under examination.

Within the last 5 years, mobile electronic devices have been used to study a wide range of psychological and behavioral phenomena in healthy and clinical populations ranging from emotional states, stress, psychopathology, and cognition to levels of physical activity, pain, diet adherence, and fatigue [21]. Given the hierarchical structure of quantitative ESM/EMA data with multiple responses recorded for each participant, multilevel growth curve modeling is an appropriate method of statistical analysis. Growth curve modeling refers to statistical methods that enable the estimation of interindividual variability in intrindividual patterns of change over time. In particular, multilevel growth curve modeling allows for the nesting of multiple repeated measures within each individual for direct estimation of a variety of powerful and flexible growth models [22]. Multilevel growth curve modeling can handle nested data with an unequal number of observations across individuals as well as irregular intervals between observations that can occur with ESM/EMA data. Various statistical programs (e.g., R, Mplus, SAS, SPSS, Stata) have multilevel modeling features that can be used to analyze ESM/EMA data. For example, Garland et al. [23] used ESM and growth curve modeling to examine the effects of mindfulness-based cognitive therapy (MBCT) on positive affect and cognition in 64 middle-aged adults in partial remission from depression. ESM assessed changes in affect and cognition for 6 consecutive days before and after MBCT or a wait-list condition, and modified growth models enabled the simultaneous estimation of time-specific autoregressive effects (i.e., control for past levels of the outcome) and cross-lagged effects (i.e., provide evidence on the direction of causality) of daily positive affect and cognition on subsequent daily levels. Garland et al. [24] found cross-lagged effects in the MBCT group of daily positive affect on subsequent affect and cognition as well as high correlations between positive cognition and same-day positive affect, which suggests an emotion-thought cycle of influence spurred by MBCT. The combination of ESM/EMA and growth curve modeling provides a robust method to analyze the patient’s subjective response to treatment and can be combined with objective behavioral, physiological, neuroendocrine, and immune measures to triangulate intervention effects.

### Wearable Smart Technologies for Measuring Stress

**Physiology and Physical Activity**

Psychological approaches provide valuable insight into perceived effects and mechanisms of IM interventions on disease processes and are greatly strengthened by coupling with objective behavioral, physiological, and biomolecular outcome measures. At a physiological systems level, the most immediate outcome measures affected by IM approaches are those of the cardiac autonomic (sympathetic and parasympathetic nervous system) and neuroendocrine [hypothalamic-pituitary-adrenal (HPA) axis] stress responses. Specific to the autonomic stress response, heart rate variability (HRV) is the most sensitive noninvasive measure currently available for calculating the relative balance of sympathetic and parasympathetic nervous system activation.

---

**Integrative Medicine Research Methods with a Focus on Aging Populations**

**Gerontology 2016;62:467–476**

DOI: 10.1159/000441494
Although the heart rate generally increases with activation of the sympathetic nervous system and stress, HRV decreases with stress and disease [25, 26]. An increase in HRV reflects activation of the parasympathetic nervous system and ‘relaxation response’ [27], through the activation of the vagus nerve, generally induced by slow, deep breathing [28]. It is well established that HRV decreases with age, at least until the sixth decade of life after which it may stabilize [29]. In addition, vagal control of heart rate is generally lower in women, though sex differences in HRV disappear by age 50 years [29]. Lower levels of parasympathetic (i.e. vagal) modulation of HRV are associated with increased cardiovascular morbidity and mortality in the elderly [30]. Higher levels of vagally modulated HRV are associated with higher levels of physical fitness, and research suggests that long-term exercise may promote healthy aging by attenuating the neural decline in vagal control of HRV [31]. Rapid advances in the development of mobile health (mHealth) devices are allowing the tracking of HRV during activities of daily living [32]. These devices also have the advantage of tracking mobility, posture, activity, and sleep quality, which comprise important aspects associated with healthy aging [33, 34].

Due to ease of measurement, heart rate-derived parameters are some of the most popular measures to track physiological stress response. The technology for measuring heart rate and HRV could be in the form of activity belts, chest-worn bioelectrodes/belts, or wristwatches. Variations in heart rate or HRV may be evaluated by various methods [35]. However, usually a series of rules (e.g. peaks detected in predefined intervals with large enough width) are required to enhance the accuracy of measurement. In general, faulty detection of a QRS complex due to sensor disconnection or noisy peaks due to artifacts like motion may not significantly change the estimated value of heart rate, but could significantly impact HRV and thus lead to misinterpretation of the physiological response to stress. Of particular relevance to the measurement of HRV in elderly populations is the potential artifact produced by an increased prevalence of random heart rate patterns and erratic rhythms. These can falsely elevate the values of short-term HRV measures, although long-term HRV measures, which are primarily influenced by circadian rhythms, are not strongly affected by such erratic rhythms [36]. Long-term HRV monitoring is recommended to reduce such artifacts, and advanced signal processing (e.g. nonlinear quantifications) could be applied, which are less impacted by erratic rhythms and more sensitive to other aging-related problems such as frailty [35]. Indeed, a systematic review by Parvaneh et al. [35] revealed that frail older adults show reduced HRV, reduced heart rate changes in response to daily activities (e.g. lying to standing postural change), and a loss of complexity in the heart rate as compared to nonfrail older adults.

One of the major shortcomings of traditional methods in the estimation of HRV is that they are not personalized and thus unable to track physiological stress fluctuation during daily living. To address this limitation, new personalized algorithms have been proposed which enable tracking changes in HRV parameters with respect to a relaxation reference status [32, 37]. For example, in a population of diabetic patients from 27 to 78 years of age with chronic wounds, Parvaneh et al. [32] demonstrated that by normalizing the standard deviation of all normal intervals between consecutive sinus beats (SDNN; time domain estimation of HRV) values measured during a wound clinic visit by the SDNN value measured during a relaxed condition, physiological stress response fluctuations during a wound clinic visit could be quantified as low stress (SDNN value >85% of relaxed SDNN), medium stress (SDNN value between 60 and 85% of relaxed SDNN), and high stress (SDNN value <60% of relaxed SDNN). Results indicate that patients experienced moderate to high stress during podiatric clinic visits for wound dressing, and such stress may negatively impact wound healing [37]. Although the results were independent of age, the study was not sufficiently powered to address the association between age and normalized SDNN.

In addition to the measurement of heart rate and HRV, advances in wearable physiological devices enable the measurement of motor performance (e.g. gait, balance, and physical activities) in routine clinical assessments as well as during activities of daily living. Until recently, the measurement of physical activity primarily consisted of simple parameters, including duration of walking or total number of daily steps. However, this information provides only a short snapshot of older adults’ daily physical activities (e.g. 3–10% of 24-hour activities) [38]. Traditional devices do not provide information about the type or patterns of movement activity, or the quality of motor tasks (e.g. sitting to standing postural transitions), which better reflect the physical health and well-being of elderly populations [38]. In contrast, recent wearable technologies allow for the extracting of fine grain information about daily physical activities (e.g. sitting, standing, and sleep quality), gait (speed and gait variability), and balance (body sway and postural coordination) [38]. For example, Najafi et al. [38] have developed a single sensor
system and the corresponding triaxial accelerometer algorithm that can track postural transition, allowing for accurate identification of elderly adults at risk of falling. Such technologies may be more sensitive to evaluate the effects of IM on motor performance. Toosizadeh et al. [12] demonstrated in a double-blind randomized control trial that wearable technologies are sensitive enough to track improvement in postural control in elderly patients with Parkinson’s disease following 3 weeks of electroacupuncture therapy. Therefore, such advanced technologies may help to overcome some of the shortcomings of previous methods assessing effects of IM on motor performance including questionnaires/diaries or imprecise assessments (e.g. step counters to estimate physical activities). In combination with psychological and biomolecular measures, wearable physiological devices produce fine grain data on physiological stress response and motor performance to quantify the effects of IM interventions in real-life ambulatory settings of older adults and patients.

**Immunochemical Methods for the Measurement of Biomarkers in Sweat**

Moving from psychological through physiological scales of measurement, the next scale that must be included in comprehensive research of IM is the molecular scale. Typically, molecular biomarkers are measured in blood plasma or, in the case of cortisol, in the saliva. This section focuses on novel and developing methods to measure molecular biomarkers noninvasively in other sources, such as sweat and hair.

In aging populations, molecular biomarkers of interest might include cytokines, C-reactive protein and other molecules of the immune and inflammatory responses, neuroendocrine measures of the HPA axis response, and salivary amylase as a reflection of sympathetic nervous system activation. Many of these biomarkers are affected by aging. Immunosenescence, the natural age-related decline of immune competence, is affected by factors like diet, exercise, and psychological stress, among others [39, 40]. In addition, research suggests that aging is associated with greater activation of the HPA axis, resulting in increased production of cortisol compared to younger adults [40]; cortisol is crucial to the regulation of the immune system, and its dysregulation is implicated in several immune-mediated diseases. Of note, basal amylase activity remains stable in older age, although acute changes in amylase due to acute stress response in older adults are unknown [41]. Therefore, molecular biomarkers provide important measures of the endocrine and immune system activity, and it is important to obtain baseline levels of relevant molecular biomarkers before and after an IM intervention (at a minimum) in order to determine intervention effects.

In addition, length of telomeres (i.e. ends of chromosomes) and levels of telomerase, the enzyme that repairs telomeres as they age, have been shown to reflect chromosomal aging and chronic stress [42]. Chromosomal telomere length typically shortens with age, such that biological age can be estimated based on telomere length in nonstressed populations [42]. Telomere shortening is greatly accelerated by chronic stress and total load of stress, termed ‘allostatic load’ [42]. Conversely, IM lifestyle change, including mindfulness meditation three times per week, Mediterranean diet, and regular exercise, have been shown to increase levels of telomerase and may even slow or help reverse the process of telomere shortening [5].

Various molecular measures can be collected to determine the effects of IM interventions on acute stress responses. Salivary cortisol is well established as an accurate noninvasive measure of free plasma cortisol and acute activation of the HPA axis [43]. Noninvasive methods to detect immune responses are less well established. Blood plasma is the most common source in molecular biomarker research, and it has been the gold standard in many medical tests. However, there are obvious disadvantages of using blood, most notably the invasive nature of drawing blood and the inability to sample continuously as individuals engage in daily activities outside of a laboratory setting. Importantly, physical and physiologic changes due to normal aging, such as thinning of dermal layers, loss of skeletal muscle mass, and small fragile subsurface blood vessels, may impede blood specimen collection in the elderly [44]. In addition, collecting blood requires that people travel to a clinical setting, or that a clinical technician travels to them. Developing noninvasive methods that can continuously measure a wide variety of molecular biomarkers in daily living would be of great advantage to the elderly who may experience difficulty leaving the home setting.

In order to accurately document the impact of IM interventions, especially outside hospital settings, noninvasive methods to detect a battery of molecular biomarkers is needed. Sweat is a promising source of neuroendocrine and immune biomarkers. In addition to electrolytes, sweat contains a wide variety of potential biomarkers such as proteins, neuropeptides, hormones, catechol-
amines, indoleamines, fatty acids, and metabolites [45–47]. These molecules may appear in sweat through multiple mechanisms, including blood filtration, secretion by sweat glands, and secretion by periglandular nerve endings. Sweat production is initiated or influenced by emotional and physical activities, such as stress, shock, fatigue, and hydration.

Recent proof-of-principal studies [45, 48] showed that a range of neuroendocrine and immune biomarkers is detectable in sweat, and that levels of these biomarkers correlate with plasma levels, as well as with symptom patterns in women with a history of major depressive disorder. Specifically, a convenience sample of women with a history of major depressive disorder, considered to be in clinical remission, nonetheless exhibited elevated proinflammatory cytokines, elevated pain neuropeptides, elevated neuropeptide Y, and decreased vasoactive intestinal polypeptide in both sweat and plasma [45]. These biomarker levels correlated with anxiety and depression scores on the Hamilton Depression and Anxiety Scales [45]. Additionally, elevated neuropeptide Y (indicative of increased sympathetic activity), decreased vasoactive intestinal polypeptide (indicative of reduced parasympathetic activity), and an underlying proinflammatory state are consistent with the known comorbidities of major depressive disorder, including diabetes, metabolic syndrome, cardiovascular disease, and osteoporosis [45].

Regarding cortisol collection, Grass et al. [49] compared hair cortisol concentrations (HCC), salivary cortisol, and cortisol in sweat as well as individuals’ sweating rate in order to examine the sensitivity of HCC to acute influences, possibly related to cortisol absorption from sweat. HCC was found to be unrelated to acute salivary cortisol reactivity, sweat cortisol levels, sweating rate, and the time of examination, thereby supporting HCC as a marker of long-term systemic cortisol secretion. On the other hand and similar to previous findings, sweat cortisol levels were positively related to total salivary cortisol output across the examined periods, indicating that cortisol levels from sweat are sensitive to acute influences. Of note, Grass et al. [49] utilized a simple method of sweat collection (cotton swab across the forehead and an absorbent pad to measure sweat rate).

Although promising, sweat presents various challenges in sampling methods and analysis. The concentration of many biomarkers in sweat is extremely low; thus, the selection of the proper sweat collection device is paramount to avoid biomarker loss. Physiological variables such as sweat rate and sweat volume differ with activity levels, and variations in sweat gland distribution in different body areas may affect sweat sample integrity. Potential biomarker degradation by protease or bacteria and food intake before sweating may also adversely affect the quality of sweat samples. However, development is underway to resolve these challenges [45–47, 50] because sweat has the potential to enable continuous monitoring of multiple biomarkers unlike blood plasma and saliva samples that are limited to a single time point.

Despite the challenges associated with sweat collection and analysis, sweat is a valuable source of sensitive biomarkers involved in multiple endocrine and immune processes. At this time, no studies on sweat biomarkers have been performed in aging populations nor have specific comparisons been performed between males and females. Such studies await further development of the technology for measuring biomarkers in sweat. With further development of sweat collection devices and analytic platforms, sweat could enable objective and noninvasive examination of system level interactions during IM interventions for disease prevention and treatment.

**Considerations and Mathematical Methods for the Analysis of Psychological, Physiological, and Biomolecular Data Collected in Ambulatory Settings**

The methods described above represent a rich new armamentarium that can aid in the assessment of IM treatment effects and mechanisms of change in aging populations. In particular, it is possible to measure changes across stress response systems, which can affect short- and long-term health outcomes [5, 42]. However, these new methods also represent a challenge to the traditional methods for quantifying stress responses, especially when the goal is to integrate the responses and measures derived from the different methods. There are at least three often neglected issues and corresponding recommendations related to the measurement of multivariable stress responses.

The first issue is related to the temporal dynamics of individual stress responses. Traditional assessment of stress responses has often relied on the so-called reactivity hypothesis. This hypothesis states that repeated large magnitude responses to discrete stressors are associated with risk for the subsequent development of stress-related disorders. Because this approach was developed in the context of laboratory-based stress assessments, it is not very well suited for the examination of stress responses during the activities of daily living. This is particularly true when ‘discrete’ stressors may be difficult to identify.
Moreover, it fails to take into account the temporal dynamics of stress responses including the anticipation and recovery from stressors. For example, Brosschot and Thayer [51] showed that the initial heart rate responses to positive as well as negative emotions were of the same magnitude. Jacob et al. [52] previously showed the same pattern for blood pressure responses. However, Brosschot and Thayer [51] also assessed the temporal dynamics of the responses and showed that whereas the heart rate response to negative emotions remained elevated in the subsequent 5-min epoch, the heart rate response to positive emotions returned to baseline levels. Assessing the temporal dynamics of the responses made it possible to disentangle the effects of the arousal dimension of emotion (which predicted the initial heart rate response) from the valence dimension of emotion (which predicted the prolonged heart rate response). In addition, numerous physiological and stress response systems show pronounced rhythmicity including circadian variations [53]. In aging populations, Loerbroks et al. [53] showed that with increasing age the circadian variation in HRV decreased such that the ‘normal’ nighttime increase in HRV was blunted. Therefore, assessing the temporal dynamics of psychological phenomena and stress response systems using ESM/EMA and wearable, noninvasive devices with consideration of age differences may yield important information about stress, well-being, IM prevention, and intervention for healthy aging.

The second often neglected issue concerns the varying time lags in response to the challenge of different stress response systems. In the ongoing flow of daily living, numerous responses occur on varying time scales across different psychological and physiological systems. For example, parasympathetic influences on the heart can occur on the order of magnitude of milliseconds, whereas the sympathetic influences occur on the order of magnitude of seconds [54]. The complexity increases when examined across response systems. In a laboratory study of recovery from a psychological stressor in healthy young males, Weber et al. [55] showed that the cardiovascular system response was on the order of magnitude of minutes, the HPA axis system response was on the order of magnitude of 10s of minutes, and the immune system response was on the order of magnitude of hours. In a study of critical care personnel at work, Looser et al. [56] compared the cortisol data with heart rate data collected 15–45 min before the cortisol sample to account for the known temporal delay between the changes in heart rate (immediate) and the changes in salivary cortisol concentrations (usually peaking 20–30 min after the onset of a stressor). Fourth, Pearson correlation coefficients are used to characterize the relationship among change scores for various measures/response systems (e.g. cortisol and heart rate). In addition, the analysis can be repeated using multilevel growth curve modeling (described above) to predict an outcome variable adding day- and person-specific covariates.

The third issue that is often overlooked is that assessment of stress responses may be conceptualized as a ‘snapshot’ from an ongoing ‘movie’ of daily living. As such, the snapshot may represent the accumulation of responses over time and their related compensatory responses. Stress responses are a multivariate, dynamic process for which single-time-point ‘snapshot’ assessment is often inadequate. For example, Pieper et al. [57] examined the cumulative effects of worry on cardiovascular responses by investigating the lead-lag relationship between self-reports of worry and heart rate and HRV.
responses in a group of middle-aged teachers. The effects of worry 2 h in the past had cumulative effects such that even though worry was not reported at a particular time, the effects of worry in the preceding 2 h could still be observed in the cardiovascular responses of the individual. Therefore, it was necessary for the researchers to record these responses continuously in order to determine the cause of the observed stress response as opposed to a ‘snapshot’ assessment that would have likely led to misattribution of the cause. Repeated-measure approaches to psychological phenomena in real time such as ESM/EMA are recommended to capture the multivariate and temporal dynamics of response to stress.

This brief overview of challenges associated with the study of ‘real life’ stress responses should serve to alert researchers to some of the pitfalls as well as some of the promises in examining IM intervention effects. Paired with appropriate sampling and statistical techniques such as ESM/EMA and multilevel growth curve modeling, psychological, physiological, behavioral, neuroendocrine, and immune data can be combined to yield rich insights into IM interventions and healthy aging.

**Mobile Health Applications**

In addition to quantifying the effects and effectiveness of IM interventions in real-life ambulatory settings, the technological advances discussed herein extend the concept of mHealth to the domain of IM treatment and prevention. Patients and health care professionals are using mHealth technology at an increasing rate [15]. As of 2013, in the United States, over half of older adults who use the Internet sought health information online [58], and nearly 1 in 5 older adults owns a smartphone [17]. Additionally, 1 in 5 smartphone owners in the United States have at least one mHealth app, monitoring factors such as physical activity, nutrition, sleep quality, and physiological variables like heart rate and blood glucose [59]. The number of older adults using technology (e.g. Internet and smartphones) is on the rise [17, 59], and the utilization of mHealth apps for monitoring health is expected to grow [59]. Thus, advances in ambulatory technologies have tremendous potential to enable patient-level maintenance and improvement of health.

Briefly, mHealth technology can serve as an IM tool to increase awareness of the interplay of mind, body, and spirit across numerous aspects of lifestyle. Mobile apps and other mHealth technologies that collect data on patients (e.g. blood pressure, heart rate, and HRV) and transmit these data to health care providers for the purpose of monitoring health are certainly helpful [15], particularly in aging populations. For example, over one third of American adults aged 65 years and older fall and suffer injury as a result [60]. In the United States, approximately USD 30 billion per year are spent treating older adults for the effects of falls, and this cost is projected to rise to USD 59.6 billion by 2020 if the rate of falls cannot be stemmed [61]. Novel wearable technology can track postural transition in elderly adults and apply an algorithm to accurately identify those at high risk of falling [15, 38, 62]. Health care providers could utilize this information to help guide treatment and family elder care planning (e.g. physical therapy and independent living vs. assisted living communities). Additionally, mHealth technology could enable patients to utilize health-monitoring data for biofeedback purposes in real time as directed by their health care providers.

Prevention and wellness benefits of IM interventions could be extended through patient participation by user-centered health monitoring technology. Participatory design and feedback methods that include older adults in the development of mHealth technologies is important to help ensure designs are easy to use and meet the desires and needs of the end user [63]. The health applications are extensive, with well-designed, user-centered monitoring technology. For example, health care providers could use behavioral health techniques to motivate behavior change and provide personalized biofeedback practices that patients can implement on their own. If an older adult with cardiovascular disease experiences a stressful event that generates emotional arousal of negative valence, known to have a prolonged effect on heart rate and blood pressure [51], the individual can be alerted to their cardiovascular reactivity and implement a relaxation breathing technique (e.g. diaphragmatic breathing) to hasten recovery and return to baseline (e.g. the real-time vagal monitoring and vagal intervention app [64]). Therefore, both provider- and patient/user-centered real-time health monitoring and application of simple to complex IM practices have the potential to prevent disease and promote holistic wellness.

**Conclusions**

Advances in technology are enabling a comprehensive assessment of IM intervention responses in aging populations through the use of broad psychological measures, unobtrusive devices for monitoring cardiovascular reac-
tivity, complex physical activity and other behavioral responses in real time, and sweat biomarker analysis. These methods are becoming increasingly prevalent in medical and research settings, though their development for the public is still in its infancy.

In medical and research settings, the methods and technologies discussed herein have the potential to delineate the effects of IM interventions if they are properly applied. Successful measurement of subjective data in IM interventions requires a broad assessment of psychological constructs and a robust method of statistical analysis such as growth curve modeling. Real-time cardiovascular monitoring entails the use of newly developed personalized algorithms to track intraindividual fluctuations in stress response activity. In addition, assessment of physical activity can be improved through novel wearable devices that enable fine grain analysis of patterns of movement and the quality of motor tasks. These approaches have particular relevance for aging adults willing to optimize their activity and other behaviors to maintain their health. Sweat biomarker analysis requires the selection of the proper sampling device and the development of analytic platforms that can manage interindividual differences in sweat activity and composition, sweat gland location, and potential biomarker degradation. Together, such methodological and technological advances can and will provide new approaches for quantifying the effects and effectiveness of IM interventions in real-life ambulatory settings, and extend the concept of mHealth to the domain of IM, prevention, and wellness. These advances in monitoring, assessing, and, ultimately, informing IM treatment and behavior change will help older adults monitor their health and maintain a healthy course of aging.

References
