UCSF
UC San Francisco Previously Published Works

Title

Long-term digital device-enabled monitoring of functional status: Implications for management of persons with Alzheimer's disease

Permalink

https://escholarship.org/uc/item/4jx6w8f9

Journal

Alzheimer's & Dementia: Translational Research & Clinical Interventions, 6(1)

ISSN

2352-8737

Authors

Manley, Natalie A

Bayen, Eléonore

Braley, Tamara L

et al.

Publication Date

2020

DOI

10.1002/trc2.12017

Copyright Information

Peer reviewed

RESEARCH ARTICLE

Long-term digital device-enabled monitoring of functional status: Implications for management of persons with Alzheimer's disease

Natalie A. Manley[1] | Eléonore Bayen[2] | Tamara L. Braley[1] | Jennifer Merrilees[2] |
Amy M. Clark[1] | Bradley Zylstra[3] | Michael Schaffer[2] | Alexandre M. Bayen[4] |
Katherine L. Possin[2] | Bruce L. Miller[2] | A. Katrin Schenk[3] | Stephen J. Bonasera[1]

[1]Division of Geriatrics, Gerontology, and Palliative Medicine, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

[2]Memory and Aging Center, Department of Neurology, University of California San Francisco, San Francisco, California, USA

[3]Department of Physics, Randolph College, Lynchburg, Virginia, USA

[4]Department of Civil and Environmental Engineering, University of California Berkeley, Berkeley, California, USA

Correspondence

Stephen J. Bonasera, Division of Geriatrics, Gerontology, and Palliative Medicine, Department of Internal Medicine, 3028 Durham Research Center II, Omaha, NE 68198-5039, USA.
Email: sbonasera@unmc.edu

Natalie A. Manley and Eléonore Bayen have contributed equally to this work.

Abstract

Introduction: Informal caregiving is an essential element of health-care delivery. Little data describes how caregivers structure care recipients' lives and impact their functional status.

Methods: We performed observational studies of community dwelling persons with dementia (PWD) to measure functional status by simultaneous assessment of physical activity (PA) and lifespace (LS). We present data from two caregiver/care-recipient dyads representing higher and average degrees of caregiver involvement.

Results: We acquired >42,800 (subject 1); >41,300 (subject 2) PA data points and >154,500 (subject 1); >119,700 (subject 2) LS data points over 15 months of near continuous observation. PA and LS patterns provided insights into the caregiver's role in structuring the PWD's day-to-day function and change in function over time.

Discussion: We show that device-enabled functional monitoring (FM) can successfully gather and display data at resolutions required for dementia care studies. Objective quantification of individual caregiver/care-recipient dyads provides opportunities to implement patient-centered care.

KEYWORDS

Alzheimer's disease, caregiver, dementia, dyad, functional status, lifespace, n-of-1 trial, physical activity, smartphone, smartwatch

1 | INTRODUCTION

Cognitive and functional losses accumulate with age and lead to increased dependency on caregivers for assistance with activities of daily living (ADLs).[1-4] Caregivers are an under-recognized pillar upon which our entire health-care system is built[5-7] but the components of effective caregiving remain poorly understood. Further, the mechanisms by which caregiving improves patient outcomes, the characteristics of strong and effective caregiver/recipient interactions, and whether the "secrets" of successful caregiving can be taught to others are unknown.

We have little insight into the day-to-day, hour-by-hour activities of care dyads. This information, at high temporal and spatial resolution, is valuable for clinicians supporting community dwelling persons with

dementia (PWDs) and their caregivers. A clinician's understanding of a dyad's day-to-day life better informs care team efforts to troubleshoot difficulties. For example, access to circadian patterns of daily activity and lifespace may facilitate early detection and identification of functional losses at a time when interventions may delay or prevent further decline.[8,9] The time required to interview a caregiver and obtain this kind of detailed information may be prohibitive under current practice models. If clinicians could visualize a dyad's daily life structure (or lack thereof), then a more informed and efficient conversation could occur during an encounter. Personalized caregiver data can support objective qualitative and quantitative feedback regarding clinical interventions performed as part of both day-to-day clinical care and single subject randomized controlled trials. In fact, it has recently been argued that dementia research might be better suited for single subject clinical trials given the complexity and individuality of each PWD.[10,11]

Dementia care requires highly individualized treatment. An N-of-1 study (single subject clinical trial[12]) is designed for data-driven, patient-centered decision making. N-of-1 trials "consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions."[13] Health providers often have limited ability to gather objective data regarding a PWD outside of the clinic. Remote functional monitoring (FM) would allow clinicians to gather sufficient high-quality objective data in a cost-effective manner. We present here the use of remote FM as a method for gathering and displaying finely detailed data for the purposes of performing clinically relevant N-of-1 studies in dementia care.

We have recently described a system to measure activity and lifespace in persons with different stages of Alzheimer's disease (AD) who received daily caregiving.[14] We focused on activity and lifespace given their association with improved health outcomes. Physical activity (PA) has been shown to benefit persons with mild cognitive impairment (MCI), AD, and other neurodegenerative disorders (albeit, see Sink et al.[15]). For example, meta-analysis of 13 randomized controlled trials with 673 total subjects confirmed the value of moderate PA on memory in patients with AD.[16] A different meta-analysis of 41 smaller clinical trials encompassing 1,696 subjects also found a significant positive association between PA and cognition.[17] Accelerometry data obtained from a Framingham cohort of 2,354 participants determined that every hour of light-intensity PA was associated with higher brain volumes as measured by magnetic resonance imaging (MRI).[18] Similarly, Makizako et al.[19] used accelerometers to quantify activity level in people with MCI, and found that moderate intensity exercise was associated with larger hippocampal volumes. In a complementary fashion, lifespace—a measure of an individual's daily excursions from the home with or without an assistive device—reflects many outcomes of critical importance in the care of persons with dementia including mobility,[20-24] functional status,[25-30] quality of life,[31-33] probability of nursing home placement,[34-36] and morbidity/mortality.[9,37-40]

Subjects were selected from Care Ecosystem, a clinical trial to examine novel approaches that improve dementia care, lower caregiver burden and stress, and manage health-care resources.[41] To accomplish this task, we repurposed Sony SW2 SmartWatches to collect step count/activity data and MotoG 16 Gb SmartPhones to collect lifespace

RESEARCH IN CONTEXT

Systematic review: Little is known about day-to-day factors influencing the lives and functioning of persons with dementia (PWD) and their informal caregivers (dyads) in the community setting. To address this important issue, we examine patterns of physical activity (PA) and lifespace of two representative subjects as collected by our functional monitoring system over a 15-month duration.

Interpretation: Our findings demonstrate that caregivers have the potential to strongly influence day-to-day PA and lifespace in PWD. This technology is also appropriate for evaluating patient adoption of lifestyle modification advice. Ultimately, this novel approach to dementia care may be a powerful tool to facilitate provision and effectiveness of patient-centered care plans.

Future directions: Future research should include (1) integrating GIS information into patterns of dyad lifespace (2) concurrent measurement of caregiver and PWD activities (3) using activity patterns to develop evidence based support strategies for care dyad health and (4) creating early warning detection algorithms to identify tipping points for intervention.

data, and developed a secure, cloud-based infrastructure to transmit, database, and analyze these data streams.[8,14] We obtained at least 10 hours of daily subject activity and lifespace data, over >15 months, for multiple PWDs. Subjects wore the SmartWatch on a daily basis, while the caregiver kept the SmartPhone nearby. Examination of subject activity and lifespace temporal patterns revealed many instances in which caregivers were likely the major factor structuring subject behavioral patterns. In this article, we provide a detailed overview of these temporal patterns of activity and lifespace in two persons with AD, with additional annotation from caregivers to further interpret these measures.

2 | METHODS

2.1 | Subjects

We selected 2 from the 27 dyads undergoing FM. One dyad had been appreciated by the study team to be extremely diligent in their adherence to the data collection protocol; they were included to represent the "ceiling" of what this approach currently may yield. The other dyad was chosen to reflect the average user's experience regarding this data collection approach.

Where subjects were judged to have capacity for consent, both caregiver and PWD provided informed consent. Where subjects were known to lack capacity for consent, we obtained caregiver and legally authorized representative (LAR) consent. Capacity for consent was

evaluated annually. Subjects who lost the capacity for consent were reconsented by LAR. This study was performed under close Institutional Review Board supervision at the University of Nebraska Medical Center.

2.2 | Activity and lifespace data collection

As detailed in Zylstra et al.,[14] subjects wore a SmartWatch2 SW (Sony) with an intrinsic 3D accelerometer used to derive step count at 15 minute resolution. We used step count as a surrogate for overall activity. Caregivers kept a MotoG 32 Gb (Motorola) SmartPhone that received SmartWatch data and (upon detection of movement) acquired Global Positioning System (GPS) coordinates measuring lifespace at 1 minute resolution. The SmartPhone transmitted both step count and GPS data through a secure cloud-based infrastructure to our study servers, where they were stored in a MySQL database. Both step count and GPS data underwent automatic quality control evaluation to identify outliers, which constituted <1% of all data collected.

2.3 | Clinical data collection and interviews

After provision of informed consent, the Care Ecosystem study team[41] obtained health-care records (including neuropsychological, laboratory, and imaging results), and scheduled telephone or face-to-face interviews with the dyad to obtain detailed descriptions of their evolving day-to-day caregiving efforts.

2.4 | Data visualization

We wrote code using MATLAB (Mathworks, Natick, MA, USA) to show daily step counts as raster plots in polar coordinates. GPS data were imported into the website www.gpsvisualizer.com to create maps of monthly lifespace. We used drawing software (Adobe Illustrator) to create perspective views of these maps.

3 | RESULTS

The first subject was a 73-year-old white woman with advanced AD. In 2004, she was first evaluated for a 2-year history of gradually progressive short-term memory loss. Her medical history was significant for Charcot-Marie-Tooth disease, mild depression, migraine headaches, obstructive sleep apnea, bilateral knee arthritis, and osteoporosis. She had a doctorate level education and a family history of AD. Her full-scale IQ was estimated at 113, verbal IQ 119, and performance IQ 103. She had normal letter verbal fluency, impaired categorical fluency, and difficulties with planning and reproduction of a complex figure. Her verbal immediate recall was in the 42nd percentile; however, her verbal delayed recall was in the 18th percentile. Her visual immediate recall

was in the 50th percentile, and her visual delayed recall was in the 27th percentile. MRI imaging of the brain and laboratory assessments (including thyroid-stimulating hormone [TSH] and vitamin B12 levels) were unremarkable.

Neuropsychological examination in 2007 suggested significant progression of her cognitive amnestic phenotype. Driving evaluation in 2010 suggested that she could not safely operate a motor vehicle. During this period, she was hospitalized once for atrial fibrillation and once for surgical repair of a wrist fracture after a fall.

At study enrollment in November 2015, she could not recognize one of her sons, became agitated in unfamiliar situations, had decreased alertness in the late afternoon, and wandered at night. She remained continent of bowel and bladder. She had moderate dementia severity by Quick Dementia Rating System (QDRS) of 12.5 (4.5 cognitive, 8 behavioral).[42] Behavioral screening (based on major categories of the Neuropsychiatric Inventory),[43] was negative for delusions, hallucinations, agitation, aggression, euphoria, disinhibition, repetitive behaviors, and positive for weight gain, irritability, apathy, and generalized anxiety. The Apathy Evaluation Scale, Clinician Version (AES-C),[44] score was 35, suggesting significant apathy. Mini Mental Status Examination (MMSE) score in August 2016 was 4/30. Her medications included sertraline, trazodone, melatonin, memantine, aspirin, metoprolol, omeprazole, fexofenadine, calcium with vitamin D, multivitamin, fish oil, lactobacillus, and alendronate. Cholinesterase inhibition had previously caused intolerable gastrointestinal side effects.

After her husband died in 2007, her 37-year-old son, a successful university educated graphic designer, moved to be her in-home caregiver. At time of study enrollment, he self-reported his health as good and denied any chronic medical conditions. He estimated spending 69 hours per week providing care. Local respite services also provided care for approximately 15 hours per week. He reported significant caregiver burden (28/48 on 12-item Zarit Burden Score),[45] did not report symptoms of major depression (3/9 items positive on PHQ-9), and self-reported high levels of self-efficacy (18/20).[46,47] However, formal assessment of social support[48] suggested that he had a relatively sparse social network to rely upon. He also reported poor sleep quality (5/24 score on Pittsburgh Sleep Quality Index [PSQI]).[49]

Figure 1 displays this subject's patterns of activity (raster plots per[50]) and lifespace and indirectly reveals how caregiver actions shaped and structured the subject's daily life. We aggregated over 42,800 PA data points and over 154,500 lifespace data points over 15 months of near continuous subject observation. The shift in activity onsets that occurred in October 2016 and in March 2017 is attributable to shifts between Central Daylight and Central Standard time. Figure 1A shows that the caregiver woke his mother at the same time every day as displayed by the occurrence of activity onsets starting at 08:30 military time on any of the four polar raster plots. The regular occurrence of a radial line of SmartPhone/SmartWatch connectivity but no PA (depicted in pink) at 11:30 am corresponded with the subject's lunch. A 45- to 60-minute period of inactivity starting around 13:00 to 13:30 (delineated across the four raster plots) corresponded to her afternoon nap.
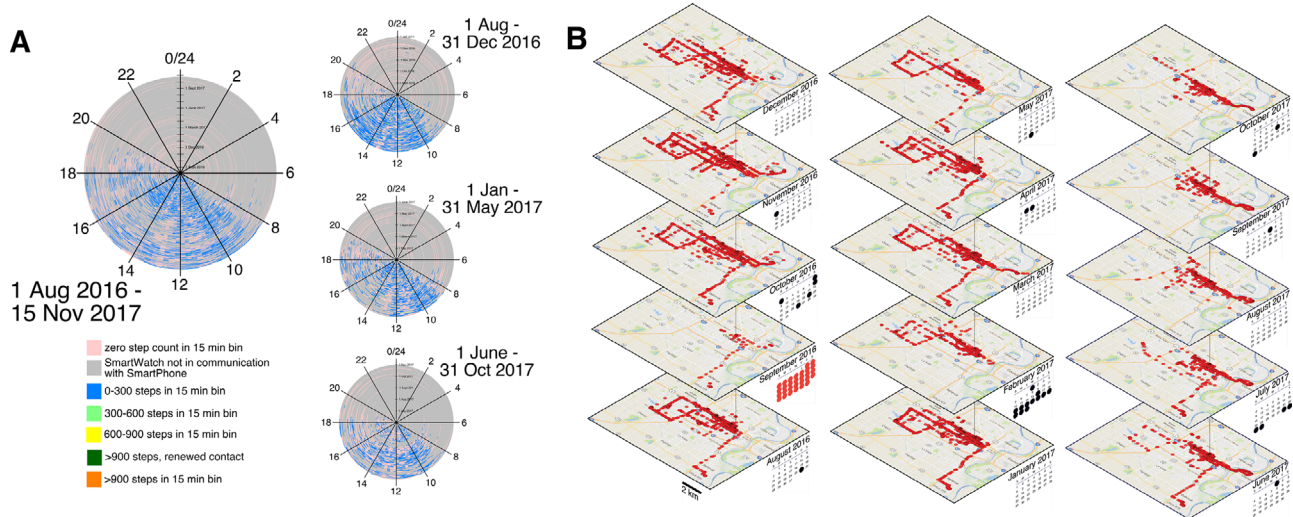
FIGURE 1 Fifteen-month activity rasters and lifespace trajectories for subject 1. A, Subject daily activity over time. Clock times are military, starting/ending at midnight. Each concentric circle represents 1 day of data collection. Early days of data collection are depicted as inner circles; later days of data collection are depicted as outer circles. Stepcount values as shown in legend and coded per colormap. The large clock on the left depicts 15 months of data collection; the smaller three clocks each depict 5 months of data spanning from August 1, 2016 to December 31, 2016 (top); January 1, 2017 to May 31, 2017 (middle); and June 1, 2017 to October 31, 2017 (bottom). B, Lifespace over 1 month epochs. Calculated from Global Positioning System (GPS) positions obtained from days for which data are available. The isometric lifespace planes are oriented to facilitate reading. The map's top corresponds to north and the map's right edge corresponds to east. Lifespace trajectories in red points; each plane depicts another month of data. Subject home depicted by the thin vertical line. Calendars adjacent to each monthly lifespace plane show days that contributed to the overall lifespace; dates blotted out by a black circle indicate no subject data for that day (likely due to subject/caregiver factors, such as not remembering to charge devices or keep cellphone on person); dates blotted out by a red circle indicate data loss due to infrastructure problems. Distance calibration provided next to plot

The subject's overall circadian activity significantly decreased in mid-February 2017 with no return to her prior baseline. This change is best appreciated by comparing clock "slices" between 12:00 and 16:00 for activity data collected between August 1, 2016 through December 31, 2016 (top small raster plot) and January 1, 2017 through May 31, 2017 (middle small raster plot). Clinical review and caregiver interview revealed no change in subject health or caregiving routine. There was no record of fall(s), worsening delirium, dizziness, worsening gait, or other geriatric syndromes. Finally, no activity data were acquired for 10 days after August 4, 2017. This period corresponded to physician-advised bedrest after diagnosis of a lumbar compression fracture.

In contrast to her activity onsets, there is a more ragged pattern of activity offsets. The irregular timing of activity offsets can be appreciated in all four raster plots. By caregiver report, his mother usually began experiencing reduced alertness and cognition around this time. After dinner (≈17:30), her caregiver started her bedtime routine. No information regarding awakenings and sleep disturbances was collected because the Smart Phone/SmartWatch were being charged at night.

The dyad's measured lifespace (binned in one-month intervals) is depicted in Figure 1B. An Android update broke data collection in September 2016, leading to incomplete lifespace acquisition for this month. Since the subject could not drive, this lifespace fully reflects the caregiver's role in shaping her day-to-day excursions. Note that all the monthly lifespaces were essentially superimposable on one another

(lifespace data collected in September 2016 also superimposes on these months, with regions of incomplete overlap). This finding indicates the caregiver structured this subject's life on a regular, repeatable, near daily basis regardless of seasonal climate changes (Table 1).

However, her lifespace decreased with time, especially after June 2017, reflecting a growing inability to participate in outside activities. Per caregiver report, she could not attend her usual adult day program (indicated by the trajectories forming a square near the top and left corners of each plane) after June 2017 because of dementia progression. She changed to a different day program (between top and bottom right corners of each plane). After July 2017, the dyad no longer traveled to church (near the bottom corner of each plane), because she could not sit through the service. QDRS obtained in November 2017 revealed a score of 24 (10 cognitive, 14 behavioral; both significant increases from her enrollment QDRS). Ultimately, with the subject's functional and cognitive decline and increasing care needs, the caregiver sought nursing home placement in January 2018.

The second subject was a 74-year-old white woman with mild to moderate AD. Her medical history included bilateral cataract removal, total hip replacement, cholecystectomy, and hysterectomy. She had a family history of dementia and sensorineural hearing loss. She earned a bachelor of science degree in nursing and worked as a clinical psychologist. She never smoked, drank, or used illicit drugs.

She was first evaluated for memory loss after a concussion without loss of consciousness in September 2009. In the days after the

TABLE 1 Outside-the-home excursions for subjects 1 and 2

Month/year	Subject 1			Subject 2		
	No. of trips	No. of days observation	No. of days no data collection	No. of trips	No. of days observation	No. of days no data collection
August 2016	27	30	1	14	22	1
September 2016	1	1	29	0	1	29
October 2016	23	25	5	11	30	1
November 2016	26	28	1	4	30	0
December 2016	27	31	0	2	25	6
January 2017	30	31	0	1	31	0
February 2017	12	19	12	10	19	9
March 2017	29	31	0	2	16	15
April 2017	28	30	2	8	30	0
May 2017	28	30	1	7	18	13
June 2017	28	29	1	10	11	19
July 2017	23	17	4	13	19	12
August 2017	30	31	0	19	27	4
September 2017	28	29	1	26	30	0
October 2017	26	29	2	26	31	0

Values manually curated by examining daily lifespace trajectories. Each trip starts and ends at subject home.

concussion, her husband noted that she was more withdrawn and had difficulty operating household items such as a microwave oven. Neurologist evaluation (including MRI) was unremarkable except for MMSE score of 21/30. Within a week of the concussion her cognition returned to prior baseline per family report.

Her husband noticed a more subtle cognitive decline over the first 10 months of 2014. She began having difficulty writing checks and using a computer. She stopped reading and self-curtailed her driving. Normally outgoing, she became shy and quiet. Neurology evaluation revealed short-term memory and word-finding deficits (MMSE was 18/30, with errors in orientation, registration, attention, calculation, recall, and language). Basic laboratory testing was unremarkable. Positron emission tomography (PET) scan revealed decreased glucose uptake throughout the right parietal cortex consistent with AD. The dyad decided to move to an assisted living facility (ALF) to be closer to family.

At study intake in May 2016 her QDRS score was 10 (4 cognitive, 6 behavioral). Behavioral screening was negative other than symptoms of apathy, irritability, craving for sweets, and trouble sleeping. Her AES-C score was 59, indicating marked apathy. Her medications included donepezil, memantine, niacin, calcium, magnesium oxide, vitamin B12, tolterodine, and a multivitamin.

The subject's husband had been her primary caregiver since the initial symptom onset. He had a master's level education with a career in public television. He reported a personal history of hypertension, gastric reflux, and hormonal therapy for non-metastatic prostate cancer.

At time of study intake he and his wife resided together in an ALF, and he estimated spending 7 hours per week on her care. They received no respite or adult day health services. He reported low caregiver burden (6/48 on 12-item Zarit Burden Score), did not report symptoms of major depression (0/9 items positive PHQ-9), and self-reported moderate levels of self-efficacy (9/20). His social support network was limited to their two adult children and cousins who lived locally. He had not cultivated any relationships within the ALF. He reported no decline in sleep quality (PSQI score 1/24).

Figure 2A shows that the subject had overall low levels of baseline activity. We aggregated over 41,300 PA data points and over 119,700 lifespace data points over 15 months of near continuous subject observation. Again, shifts to and from Central Daylight/Standard time occurred during data collection. The earliest activity onsets corresponded to about 10:00 am (showering and dressing). We did not capture her breakfast meal at 7:00 am, because she did not wear the SmartWatch until after her shower. There was a regular pattern of activity preceding noon corresponding to when the ALF served lunch. After lunch, the dyad took a 30-minute walk before returning to their apartment. From 2:00 to 4:00 pm, the subject showed the greatest degree of PA, corresponding to the dyad doing errands or participating in structured ALF activities. Activity offset usually occurred around 23:00, with minimal activity in the preceding six hours. Her activity profiles remained similar throughout the 15 month observation period. Overall, this subject's activity patterns suggested that on her own, she was likely to remain inactive, and that her activity levels only increased for events such as meals, or through direct encouragement of her caregiver. Because the subject was not wearing the SmartWatch at night, we were unable to detect episodes of nighttime wandering (which occurred more frequently over time).

Examination of this subject's lifespace (Figure 2B, binned in 1 month intervals and also affected by the September 2016 Android update) provides further data supporting the caregiver's role in shaping subject day-to-day experiences. This subject did not drive, so her lifespace depended upon her caregiver. During August 2016 she displayed a varied lifespace (Table 1). However, lifespaces for September 2016 through March 2017 were more constricted (Table 1). The caregiver attributed much of this decrease in monthly lifespace to the onset of colder weather, and a lack of routine planned activities occurring outside the ALF. Fewer trips outside of the ALF during this period translated into fewer opportunities to reinforce daily living skills. The caregiver recognized that his wife could benefit from increased socialization, and thus moved to a different ALF in January 2016. This event can be appreciated by the shift in the home base location in the dyad's lifespace trajectories. In April 2017 our team advised the caregiver to increase his wife's monthly lifespace. He followed this suggestion, with larger lifespaces observed in April through October 2017 (Table 1). QDRS assessment April 2017 revealed a score of 18 (10 cognitive, 8 behavioral, both a significant increase from her enrollment status).

Ultimately, with the subject's worsening urinary and bowel incontinence, the caregiver elected to transfer his wife to the dementia unit within their ALF in January 2018.
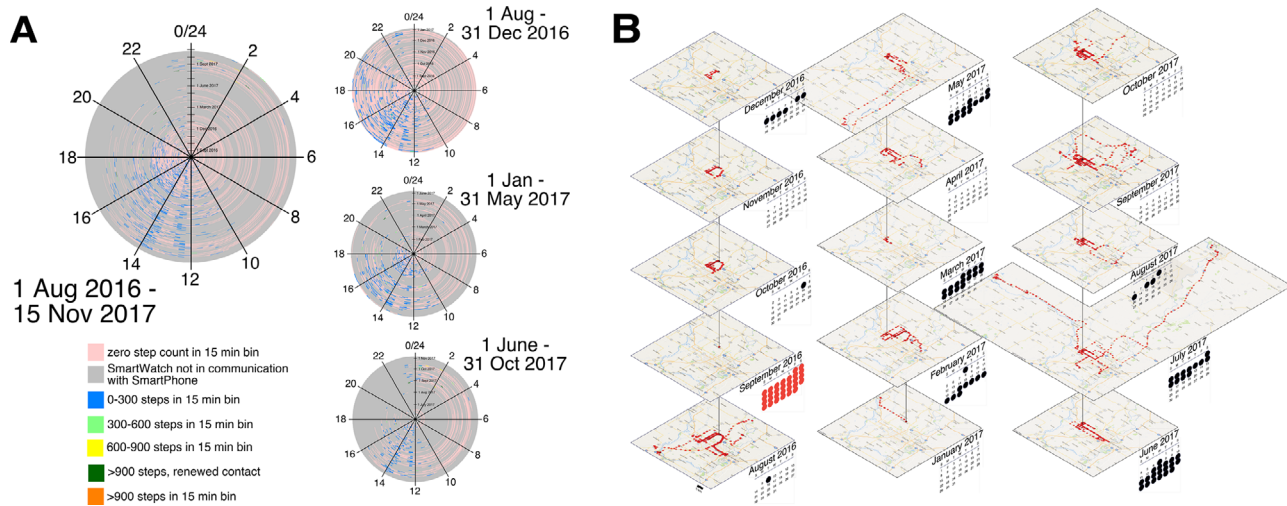
FIGURE 2 15-month activity rasters and lifespace trajectories for subject 2. Figure organization per Figure 1

4 | DISCUSSION

This study shows how massive data sets collected for a single subject may be leveraged for clinical trials, especially single subject clinical trials. In traditional clinical trials, investigators ensure trial reproducibility by evaluating outcomes in large subject cohorts such that statistical power (both α and β) is achieved at a given detection threshold.[51,52] However, clinical trial per-subject enrollment costs are often the limiting factor driving trial recruitment[53,54] leading to underpowered studies unable to demonstrate differences between treatment groups. In the complex setting of dementia care, we argue there is benefit to obtaining frequent repeated measures from a single subject to support robust intra-subject comparisons. Despite expected individual variability in daily, weekly, or monthly activity, and lifespace, these large data sets (Figures 1 and 2) accurately depict subject activity and lifespace baselines while providing the boundaries of expected variation. Furthermore, individual differences are clearly appreciated, thus allowing for group comparisons or within-individual longitudinal comparisons.

Functional monitoring can both improve the rigor and reproducibility of many outcomes currently used in studies of dementia, as well as open the possibilities for novel outcomes that will extend our knowledge of how PWD interact with their caregivers. This will further guide interventions designed to prevent functional loss. At first iteration, functional monitoring provides highly rigorous and robust measures of overall PA and lifespace, two important aspects of function that are challenging to collect in the field.[55-57] These measures do not depend on individual or caregiver recall[58,59] and further represent subject performance over extended durations of time. Future studies may consider integrating results of these measurements with traditional genetic and neuroimaging data to test novel hypotheses regarding how specific genetic loci or neuroanatomical changes lead to loss of PA/lifespace. This technology may also lower the cost for larger scale studies of circadian behaviors in PWDs.

Functional monitoring technologies will also facilitate novel studies examining interactions between caregivers and PWDs in greater detail than currently possible. It is well established that caregivers play a critical role in ensuring PWD care and quality of life.[60-62] However, most ethologic studies of caregiving rely on subject-provided outcome measures[63,64] and are thus subject to observational biases. Functional monitoring technology provides a minimally invasive manner for probing dyad interrelationships, quantifying established PWD routines (as shown in this work), quantifying times in which caregiver and PWD are in close proximity, and examining how lifespace factors (access to nearby entertainment, shopping, health care centers, for example) facilitate or inhibit PWD use of community resources.

Most intriguingly, functional monitoring approaches may identify PWDs at immediate risk for upcoming functional loss. Functional status trajectories have been best modeled as nonlinear systems.[65-67] These models are highly similar to those of climate change, desertification, and similar ecological events in which investigators have successfully identified potential system "tipping points."[68-70] Tipping points, which are regions of state space in which a system may transition between two stable states, may be identified by examining time series features, including autocorrelation, variance, return time, and skewness.[71] Time series data such as that presented here will thus be critical for resilience mapping of individual functional status,[72] as well as identification of impending "tipping points" in functional status.[73,74] As each PWD is his/her own control, these tipping points represent situations in which the PWD may be at high risk of impending, and possibly irreversible, functional loss.

We stress the potential utility of such connected data both clinically and in research trials to (1) provide an objective summary picture of the often unwitnessed co-functioning of care dyads, (2) to allow for inference into unmet needs of the dyad, and (3) to monitor response to clinical or educational interventions. For example, data presented in this article strongly suggest that caregiver activity has the potential to significantly affect PWD activity (Figures 1 and 2). Future studies examining activity of PWD in response to specific interventions thus need to take caregiver activity into account. Various means of adjusting PWD activity for caregiver activity might be considered, including

differentiating PWD activity by proximity to caregiver; developing algorithms to identify stereotypic, repetitive behaviors in PWD PA data; and examining the probability of PWD PA as a function of caregiver activity through t-patterns,[75] among others.

The first dyad in this study lived a more structured and active day-to-day life than the second dyad. While both subjects are similarly apathetic and subject 1 more severely impaired, the caregiver of subject 1 maintained higher monthly step counts and more extensive lifespace for his care recipient than the caregiver of subject 2. This illustrates how much caregivers can shape their care recipients' lives, and conversely how much PWD rely on their caregiver's motivation or capabilities. Well maintained lifespaces suggest that the PWD regularly participates in the ADLs required for leaving the home (eg, toileting, dressing). This participation reinforces the motor/habitual memory systems that are relatively intact in AD[76] as well as providing opportunities for regular PA. This research shows the meaningfulness of a holistic approach toward the care dyad[77] because a PWD's activities and health status are highly connected with the caregiver's actions (and vice versa).

There are limitations to these FM methods that could be remedied with future technology. The device needed to be charged at night leading to a loss of nighttime wakening information. There is also a dependence on the telecommunications service provider with possible lapse of service and loss of data. The present system was also not designed to provide real time monitoring or detect acute events such as falls. Our approach is currently insensitive to development of other important clinical features, such as incontinence. These limitations could be addressed in future studies by incorporating complementary approaches to acquire functional status data. For example, in home mobility data could be also obtained by a network of independently powered in-home sensors (eg, motion and magnetic contact sensors). Investigators in the ORCATECH group have successfully used this approach to obtain continuous and unobtrusive monitoring of gait, mobility, and night-time activity within the home.[78-81] Similarly, sensors for moisture[82,83] and pressure[84-86] could be integrated into these kinds of systems to assess incontinence and sleep quality. Continued advances in telecommunication technologies, particularly regarding increased battery life and "on-the-fly" charging, will make sensor-based data collection approaches even more reliable and robust.[87] Additional user-guided design changes (making the strap more difficult for demented persons to remove, etc) will also improve both data collection adherence as well as user experience. Despite current limitations, FM provides a novel view into the daily lives of the dyad that is inexpensive and currently feasible to obtain.

Recommendations for future research include (1) overlaying Geographic Information Systems (GIS) information onto GPS coordinates to infer the nature of a given trip (medical appointments vs leisure time/shopping, etc); (2) normalizing lifespace to clinically relevant environmental features such as neighborhood economic and educational status, and degree of built infrastructure; (3) performing concurrent measurement of caregiver and PWD daily life activities (to distinguish joined/shared vs separate activities); (4) using activity patterns to develop evidence based support strategies for caregiver and care-recipient health; and (5) adapting currently available early warning detection algorithms to identify tipping points for early intervention.

In summary, policymakers and health professionals agree that caregivers constitute a vital labor force whose work critically shapes care outcomes and may either delay or prevent long-term institutionalization of PWDs.[88] Understanding caregiver burden and/or uncovered needs to avoid burnout or withdrawal from the caregiving role remains a critical task.[89,90] Care dyad function and dysfunction over daily, monthly, and often annual time windows has been very difficult information to collect. Our connected caregiving data enabled us to explore the home "black box" to promote data driven N-of-1 clinical trials with patient-centered interventions and ultimately support PWD and their caregivers.

CONFLICTS OF INTEREST

Stephen J. Bonasera and A. Katrin Schenk have been granted US patent 9106718 ("Lifespace data collection from discrete areas") describing the underlying technology of our functional monitoring approach, particularly with focus on lifespace data collection/analysis.

AUTHOR CONTRIBUTIONS

A. Katrin Schenk, Alexandre M. Bayen, Katherine L. Possin, Bruce L. Miller, Stephen J. Bonasera developed study concepts and oversaw project tasks. Tamara L. Braley, Amy M. Clark oversaw system deployment to subjects. Bradley Zylstra, Michael Schaffer managed study data. A. Katrin Schenk, Stephen J. Bonasera performed data analysis. Eléonore Bayen, Natalie A. Manley, Stephen J. Bonasera, A. Katrin Schenk, Tamara L. Braley, Amy M. Clark, Jennifer Merrilees prepared the manuscript.

REFERENCES

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2224-2260.

2. Smith AK, Walter LC, Miao Y, Boscardin WJ, Covinsky KE. Disability during the last two years of life. *JAMA Intern Med*. 2013;173:1506-1513.

3. Wallace E, Salisbury C, Guthrie B, Lewis C, Fahey T, Smith SM. Managing patients with multimorbidity in primary care. *BMJ*. 2015;350:h176.

4. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med*. 2002;162:2269-2276.

5. Arno PS, Levine C, Memmott MM. The economic value of informal caregiving. *Health Aff*. 1999;18:182-188.

6. Bookman A, Harrington M. Family caregivers: a shadow workforce in the geriatric health care system? *J Health Polit Policy Law*. 2007;32:1005-1041.

7. Donelan K, Hill CA, Hoffman C, et al. Challenged to care: informal caregivers in a changing health system. *Health Aff*. 2002;21:222-231.

8. Schenk AK, Witbrodt BC, Hoarty CA, et al. Cellular telephones measure activity and lifespace in community-dwelling adults: proof of principle. *J Am Geriatr Soc*. 2011;59:345-352.

9. Xue QL, Fried LP, Glass TA, Laffan A, Chaves PH. Life-space constriction, development of frailty, and the competing risk of mortality: the Women's Health and Aging Study I. *Am J Epidemiol*. 2008;167:240-248.

10. Arnold SE, Betensky RA. Multicrossover randomized controlled trial designs in Alzheimer disease. *Ann Neurol*. 2018;84:168-175.

11. Dodge HH, Zhu J, Mattek NC, Austin D, Kornfeld J, Kaye JA. Use of high-frequency in-home monitoring data may reduce sample sizes needed in clinical trials. *PLoS One*. 2015;10:e0138095.

12. Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Schork NJ. The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? *Per Med*. 2011;8:161-173.

13. Alpi KM, Evans JJ. Distinguishing case study as a research method from case reports as a publication type. *J Med Libr Assoc*. 2019;107:1-5.

14. Zylstra B, Netscher G, Jacquemot J, et al. Extended, continuous measures of functional status in community dwelling persons with Alzheimer's and related dementia: infrastructure, performance, trade-offs, preliminary data, and promise. *J Neurosci Methods*. 2018;300:59–67.

15. Sink KM, Espeland MA, Castro CM, et al. Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults: the LIFE Randomized Trial. *JAMA*. 2015;314:781-790.

16. Jia RX, Liang JH, Xu Y, Wang YQ. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. *BMC Geriatr*. 2019;19:181.

17. Gheysen F, Poppe L, DeSmet A, et al. Physical activity to improve cognition in older adults: can physical activity programs enriched with cognitive challenges enhance the effects? A systematic review and meta-analysis. *Int J Behav Nutr Phys Act*. 2018;15:63.

18. Spartano NL, Davis-Plourde KL, Himali JJ, et al. Association of accelerometer-measured light-intensity physical activity with brain volume: the framingham heart study. *JAMA Netw Open*. 2019;2:e192745.

19. Makizako H, Liu-Ambrose T, Shimada H, et al. Moderate-intensity physical activity, hippocampal volume, and memory in older adults with mild cognitive impairment. *J Gerontol A Biol Sci Med Sci*. 2015;70:480-486.

20. Crowe M, Andel R, Wadley VG, Okonkwo OC, Sawyer P, Allman RM. Life-space and cognitive decline in a community-based sample of African American and Caucasian older adults. *J Gerontol A Biol Sci Med Sci*. 2008;63:1241-1245.

21. James BD, Boyle PA, Buchman AS, Barnes LL, Bennett DA. Life space and risk of Alzheimer disease, mild cognitive impairment, and cognitive decline in old age. *Am J Geriatr Psychiatry*. 2011;19:961-969.

22. Tsutsumimoto K, Doi T, Shimada H, et al. Self-reported exhaustion is associated with small life space in older adults with mild cognitive impairment. *J Phys Ther Sci*. 2014;26:1979-1983.

23. Uemura K, Shimada H, Makizako H, et al. Factors associated with life-space in older adults with amnestic mild cognitive impairment. *Geriatr Gerontol Int*. 2013;13:161-166.

24. Ullrich P, Werner C, Bongartz M, Kiss R, Bauer J, Hauer K. Validation of a modified life-space assessment in multimorbid older persons with cognitive impairment. *Gerontologist*. 2019;59:e66-e75.

25. Baker PS, Bodner EV, Allman RM. Measuring life-space mobility in community-dwelling older adults. *J Am Geriatr Soc*. 2003;51:1610-1614.

26. Barnes LL, Wilson RS, Bienias JL, et al. Correlates of life space in a volunteer cohort of older adults. *Exp Aging Res*. 2007;33:77-93.

27. Parker M, Baker PS, Allman RM. A life-space approach to functional assessment of mobility in the elderly. *J Gerontological Soc Work*. 2002;35:35-55.

28. Peel C, Sawyer Baker P, Roth DL, Brown CJ, Brodner EV, Allman RM. Assessing mobility in older adults: the UAB Study of Aging Life-Space Assessment. *Phys Ther*. 2005;85:1008-1119.

29. Portegijs E, Rantakokko M, Viljanen A, Sipila S, Rantanen T. Identification of older people at risk of ADL disability using the life-space assessment: a longitudinal cohort study. *J Am Med Dir Assoc*. 2016;17:410-414.

30. Ritchie CS, Locher JL, Roth DL, McVie T, Sawyer P, Allman R. Unintentional weight loss predicts decline in activities of daily living function and life-space mobility over 4 years among community-dwelling older adults. *J Gerontol A Biol Sci Med Sci*. 2008;63:67-75.

31. Bentley JP, Brown CJ, McGwin G, Jr, Sawyer P, Allman RM, Roth DL. Functional status, life-space mobility, and quality of life: a longitudinal mediation analysis. *Qual Life Res*. 2013;22:1621-1632.

32. Rantakokko M, Iwarsson S, Slaug B, Nilsson MH. Life-space mobility in Parkinson's disease: associations with motor and non-motor symptoms. *J Gerontol A Biol Sci Med Sci*. 2019;74:507-512.

33. Rantakokko M, Portegijs E, Viljanen A, Iwarsson S, Kauppinen M, Rantanen T. Changes in life-space mobility and quality of life among community-dwelling older people: a 2-year follow-up study. *Qual Life Res*. 2016;25:1189-1197.

34. Brown CJ, Kennedy RE, Lo AX, Williams CP, Sawyer P. Impact of emergency department visits and hospitalization on mobility among community-dwelling older adults. *Am J Med*. 2016;129:1124.e9-1124.e15.

35. Fathi R, Bacchetti P, Haan MN, Houston TK, Patel K, Ritchie CS. Life-space assessment predicts hospital readmission in home-limited adults. *J Am Geriatr Soc*. 2017;65:1004-1011.

36. Sheppard KD, Sawyer P, Ritchie CS, Allman RM, Brown CJ. Life-space mobility predicts nursing home admission over 6 years. *J Aging Health*. 2013;25:907-920.

37. Boyle PA, Buchman AS, Barnes LL, James BD, Bennett DA. Association between life space and risk of mortality in advanced age. *J Am Geriatr Soc*. 2010;58:1925-1930.

38. Kennedy RE, Sawyer P, Williams CP, et al. Life-space mobility change predicts 6-month mortality. *J Am Geriatr Soc*. 2017;65:833-838.

39. Lo AX, Brown CJ, Sawyer P, Kennedy RE, Allman RM. Life-space mobility declines associated with incident falls and fractures. *J Am Geriatr Soc*. 2014;62:919-923.

40. Mackey DC, Cauley JA, Barrett-Connor E, et al. Life-space mobility and mortality in older men: a prospective cohort study. *J Am Geriatr Soc*. 2014;62:1288-1296.

41. Possin KL, Merrilees J, Bonasera SJ, et al. Development of an adaptive, personalized, and scalable dementia care program: early findings from the Care Ecosystem. *PLoS Med*. 2017;14:e1002260.

42. Galvin JE. The quick dementia rating system (Qdrs): a rapid dementia staging tool. *Alzheimers Dement (Amst)*. 2015;1:249-259.

43. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44:2308-2314.

44. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. *Psychiatry Res*. 1991;38:143-162.

45. Bedard M, Molloy DW, Squire L, Dubois S, Lever JA, O'Donnell M. The Zarit Burden Interview: a new short version and screening version. *Gerontologist*. 2001;41:652-657.

46. Merrilees JJ, Bernstein A, Dulaney S, Heunis J, Walker R, Rah E, …, Feuer J. The Care Ecosystem: promoting self-efficacy among dementia family caregivers. *Dementia*. 2018:1471301218814121.

47. Steffen AM, McKibbin C, Zeiss AM, Gallagher-Thompson D, Bandura A. The revised scale for caregiving self-efficacy: reliability and validity studies. *J Gerontol B Psychol Sci Soc Sci*. 2002;57:P74-P86.

48. Grootaert C, Van Bastelaer T. Understanding and Measuring Social Capital: A Multidisciplinary Tool for Practitioners. Washington: World Bank; 2002.

49. Buysse DJ, Reynolds CF, 3rd MonkTH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193-213.

50. Campbell IH, Austin D, Hayes TL, et al. Measuring changes in activity patterns during a norovirus epidemic at a retirement community. *Conf Proc IEEE Eng Med Biol Soc*. 2011;2011:6793-6796.

51. Gabler NB, Duan N, Liao D, Elmore JG, Ganiats TG, Kravitz RL. Dealing with heterogeneity of treatment effects: is the literature up to the challenge?. *Trials*. 2009;10:43.

52. Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials*. 2010;11:85.

53. Eisenstein EL, Collins R, Cracknell BS, et al. Sensible approaches for reducing clinical trial costs. *Clin Trials*. 2008;5:75-84.

54. Information CE. Clinical Development and Trial Operations. Research Triangle Park: Cutting Edge Information; 2013.

55. LaPorte RE, Montoye HJ, Caspersen CJ. Assessment of physical activity in epidemiologic research: problems and prospects. *Public Health Rep*. 1985;100:131-146.

56. Straiton N, Alharbi M, Bauman A, et al. The validity and reliability of consumer-grade activity trackers in older, community-dwelling adults: a systematic review. *Maturitas*. 2018;112:85-93.

57. Siordia C. A critical analysis of the internal logic in the Life-Space Assessment (LSA) composite score and suggested solutions. *Clin Rehabil*. 2016;30:604-616.

58. Sallis JF, Saelens BE. Assessment of physical activity by self-report: status, limitations, and future directions. *Res Q Exerc Sport*. 2000;71:S1-14.

59. Wan N, Qu W, Whittington J, et al. Assessing smart phones for generating life-space indicators. *Environ Plann B Plann Des*. 2013;40:350-361.

60. Schulz R, Martire LM. Family caregiving of persons with dementia: prevalence, health effects, and support strategies. *Am J Geriatr Psychiatry*. 2004;12:240-249.

61. Gillick MR. The critical role of caregivers in achieving patient-centered care. *JAMA*. 2013;310:575-576.

62. Raschick M, Ingersoll-Dayton B. The costs and rewards of caregiving among aging spouses and adult children. *Fam Relat*. 2004;53:317-325.

63. Lyons KS, Zarit SH, Sayer AG, Whitlatch CJ. Caregiving as a dyadic process: perspectives from caregiver and receiver. *J Gerontol B Psychol Sci Soc Sci*. 2002;57:P195-P204.

64. Whitlatch CJ, Judge K, Zarit SH, Femia E. Dyadic intervention for family caregivers and care receivers in early-stage dementia. *Gerontologist*. 2006;46:688-694.

65. Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci*. 2009;64:1049-1057.

66. Kang HG, Costa MD, Priplata AA, et al. Frailty and the degradation of complex balance dynamics during a dual-task protocol. *J Gerontol A Biol Sci Med Sci*. 2009;64:1304-1311.

67. Lipsitz LA, Goldberger AL. Loss of 'complexity' and aging. Potential applications of fractals and chaos theory to senescence. *JAMA*. 1992;267:1806-1809.

68. Dakos V, Bascompte J. Critical slowing down as early warning for the onset of collapse in mutualistic communities. *Proc Natl Acad Sci U S A*. 2014;111:17546-17551.

69. Seekell DA, Carpenter SR, Pace ML. Conditional heteroscedasticity as a leading indicator of ecological regime shifts. *Am Nat*. 2011;178:442-451.

70. Pace ML, Batt RD, Buelo CD, et al. Reversal of a cyanobacterial bloom in response to early warnings. *Proc Natl Acad Sci U S A*. 2017;114:352-357.

71. Dakos V, Carpenter SR, Cline T, Lahti L.Early warning signals toolbox for detecting critical transitions in timeseries. Version1.0.59 ed: FreeBSD; 2013.

72. Dakos V, Carpenter SR, van Nes EH, Scheffer M. Resilience indicators: prospects and limitations for early warnings of regime shifts. *Phil Trans R Soc B*. 2015;370:20130263.

73. Kefi S, Guttal V, Brock WA, et al. Early warning signals of ecological transitions: methods for spatial patterns. *PLoS One*. 2014;9: e92097.

74. Scheffer M, Bascompte J, Brock WA, et al. Early-warning signals for critical transitions. *Nature*. 2009;461:53-59.

75. Magnusson MS. Hidden real-time patterns in intra-and inter-individual behavior: description and detection. *Eur J Psychol Assess*. 1996;12:112-123.

76. Dick MB, Shankle RW, Beth RE, Dick-Muehlke C, Cotman CW, Kean ML. Acquisition and long-term retention of a gross motor skill in Alzheimer's disease patients under constant and varied practice conditions. *J Gerontol B Psychol Sci Soc Sci*. 1996;51: 103-111.

77. Braun M, Scholz U, Bailey B, Perren S, Hornung R, Martin M. Dementia caregiving in spousal relationships: a dyadic perspective. *Aging Ment Health*. 2009;13:426-436.

78. Hayes TL, Abendroth F, Adami A, Pavel M, Zitzelberger TA, Kaye JA. Unobtrusive assessment of activity patterns associated with mild cognitive impairment. *Alzheimers Dement*. 2008;4:395-405.

79. Kaye J, Mattek N, Dodge H, et al. One walk a year to 1000 within a year: continuous in-home unobtrusive gait assessment of older adults. *Gait Posture*. 2012;35:197-202.

80. Austin D, Cross RM, Hayes T, Kaye J. Regularity and predictability of human mobility in personal space. *PLoS One*. 2014;9:e90256.

81. Petersen J, Austin D, Kaye JA, Pavel M, Hayes TL. Unobtrusive in-home detection of time spent out-of-home with applications to loneliness and physical activity. *IEEE J Biomed Health Inform*. 2014;18:1590-1596.

82. Nilsson HE, Sidén J, Gulliksson M. An incontinence alarm solution utilizing RFID based sensor technology. IEEE Xplore. IEEE. IEEE International Conference on RFID-Technologies and Applications; 2011:359-363.

83. Tanaka A, Utsunomiya F, Douseki T. A wireless self-powered urinary incontinence sensor system. *SICE J Control Measurement System Integration*. 2012;5:8-12.

84. Kortelainen JM, Mendez MO, Bianchi AM, Matteucci M, Cerutti S. Sleep staging based on signals acquired through bed sensor. *IEEE Trans Inf Technol Biomed*. 2010;14:776-785.

85. Kogure T, Shirakawa S, Shimokawa M, Hosokawa Y. Automatic sleep/wake scoring from body motion in bed: validation of a newly developed sensor placed under a mattress. *J Physiol Anthropol*. 2011;30:103-109.

86. Paalasmaa J, Waris M, Toivonen H, Leppäkorpi L, Partinen M. Unobtrusive online monitoring of sleep at home. IEEE Xplore. IEEE. Annual

International Conference of the IEEE Engineering in Medicine and Biology Society; 2012:3784-3788.

87. Boissy P, Blamoutier M, Briere S, Duval C. Quantification of free-living community mobility in healthy older adults using wearable sensors. *Front Public Health.* 2018;6:216.

88. Callahan CM. Alzheimer's disease: individuals, dyads, communities, and costs. *J Am Geriatr Soc.* 2017;65:892-895.

89. Novais T, Dauphinot V, Krolak-Salmon P, Mouchoux C. How to explore the needs of informal caregivers of individuals with cognitive impairment in Alzheimer's disease or related diseases? A systematic review of quantitative and qualitative studies. *BMC Geriatr.* 2017;17:86.

90. Ryan KA, Weldon A, Huby NM, et al. Caregiver support service needs for patients with mild cognitive impairment and Alzheimer disease. *Alzheimer Dis Assoc Disord.* 2010;24:171-176.