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Midlife Activity Predicts Risk of Dementia in Older Male Twin Pairs

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Abstract

Background—Prospective study of dementia to elucidate mechanisms of disease risk factors amenable to modification and specifically to determine whether midlife cognitive and physical leisure activities are associated with delayed onset or reduced risk of dementia within older male twin pairs.

Method—Co-twin control design using prospectively collected exposure information to predict risk of dementia 20–40 years later.

Setting—Community-dwelling and nursing home residents living throughout the continental United States.

Participants—147 male twin-pairs who were discordant for dementia or age of dementia onset and were members of the NAS-NRC Twin Registry of World War II veterans and participants in the Duke Twins Study of Memory in Aging.

Main Outcome Measure—Diagnosed dementia using a two-stage screen and full clinical evaluation. Conditional odds ratios were estimated for the association between midlife leisure activities and late life dementia.

Results—Greater midlife cognitive activity was associated with a 26% risk reduction for dementia onset. Protective effects were most robust in monozygotic twin-pairs, where genetic and early-life influences were most tightly controlled, and for activities that were often cognitive and social in nature. Cognitive activity was particularly protective among monozygotic twin-pairs carrying the APOE4 allele, with a 30% risk reduction. Midlife physical activity did not modify dementia risk.

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Conclusions—Participation in a range of cognitively and socially engaging activities in midlife reduced risk for dementia and AD in twins discordant for onset, particularly among twin-pairs at elevated genetic risk, and may be indicative of an enriched environment.

Keywords

dementia; midlife activity; leisure activity; twins

Introduction

The adage, “use it or lose it”, as applied to cognition holds great intuitive appeal to a growing population of aging individuals and suggests that cognitively enriching activity in mid- and later- life will boost one's “cognitive reserve.” This view has been supported by a number of epidemiologic studies suggesting that exposure to enriched environments may have measurable effects on cognition, and risk for age-related neurodegenerative conditions, such as Alzheimer's disease (AD) [1], [2], [3]. These studies, however, are based largely on observational data of leisure activities in older adults and cannot rule out the reciprocal possibility that those with greater reserve select more complex and cognitively challenging activities [4], [5]. Furthermore, it is difficult to separate the effects of activity from other early environmental factors known to influence cognitive reserve, such as socioeconomic status and education [6]. Finally, retrospective assessment of midlife activity is subject to recall bias. As a result, studies are often limited in their ability to differentiate the reciprocal relationships between midlife activity and dementia risk.

Co-twin control analyses address some of these difficulties by controlling for some or all genetic factors and many key early life environmental factors associated with the predictor and the outcomes of interest (i.e., AD). Twins are typically similar with respect to intellectual abilities and share a common environment into adulthood. Some of the other challenges can be addressed by collecting information on lifestyle activity in early adulthood prior to the onset of insidious neurodegenerative disorders that may in turn restrict or otherwise alter activity. Using such a design, one twin study observed protective associations between midlife activity and reduced risk within female twin-pairs discordant for AD, but not among male twin pairs [7]. The effects of midlife cognitive activity in men may be better reflected by occupation [8], [9], or, they may exert less influence than genetic mediation of risk.

The co-twin study design will be equally informative to understand the role of physical activity and risk for dementia. Leisure-time physical activity throughout life has been shown to be protective against late-life cognitive decline and AD in some studies [10], [11], [12], [13], but not in others [14], [15], [16].

We examined the association between midlife activity and subsequent risk for dementia in members of the National Academy of Sciences- National Research Center (NAS- NRC) Twin Registry of male World War II veterans. We hypothesized that greater midlife cognitive activity would be associated with lower risk of dementia or later age of dementia onset within twin pairs.

Design and Methods

Participants

Participants were enrolled in the Duke Twins Study of Memory in Aging, and were members of the National Academy of Sciences-National Research Council (NAS-NRC) Registry of World War II veteran male twins. The NAS-NRC Twin Registry was

constructed in the mid-1950's using information from vital statistics offices in 42 states to identify white male twin pairs born in the years 1917–1927. The 54,000 pairs identified were estimated to represent 93% of the white male twin pairs born during this time period in the United States. Birth certificates from these individuals were then matched to Department of Veterans Affairs files to determine veteran status, resulting in 15,924 pairs which made up the original NAS-NRC Twin Registry [17]. In 1967, questionnaires collecting information on health and activities were mailed to those pairs in which both twins were thought to be alive. The response rate to this questionnaire was 84% overall and both members of 4700 pairs responded. A total of 2112 of these individuals died from 1926 through 1966 and another 6750 died prior to 1990 [17]. Based on a multi-step cognitive screening and dementia assessment protocol conducted from 1990–2005 (described below), a total of 316 twin pairs were identified in which at least one twin was diagnosed with dementia and the other twin remained non-demented for at least 3 years after onset of dementia in the first twin. For 147 of these 316 pairs, both twins also completed a mail-in questionnaire in 1967 and were included in the present analyses. Zygosity was determined by buccal or blood DNA in 60 twin pairs and in 87 pairs from the best available information from questionnaire responses, fingerprint analysis, and anthropometric data from military records [18], [19]. The latter method of establishing zygosity was estimated by cross-validation to be 97% correct [20]. Sixty one percent of the pairs were monozygotic. All participants provided IRB-approved, informed consent prior to participation.

Outcome

The multi-step cognitive screening and assessment protocol and the number of individuals who completed each phase of the protocol are described in detail elsewhere [21]. Briefly, the 50-point Telephone Interview for Cognitive Status-modified (TICS-m) [22] was administered every 3 to 4 years from 1990–2002. When individuals could not complete the phone interview for any cognitive or physical reason, either the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [23] or another brief proxy interview was administered to a proxy, typically the wife or an adult child, asking about the participant's cognitive status. Predetermined cutpoints on each measure were used to identify individuals with suspected cognitive impairment. For the TICS-m, the cutpoint was an education-adjusted score of less than 28 on the first two waves of cognitive screening; this was increased to an education-adjusted score of less than 29 on the last two waves of screening to account for improvement due to retesting. We used the published cutpoint of 3.27 [24] for the IQCODE; for the other proxy instrument, a physician or psychologist reviewed the answers provided and determined whether the participant had suspected cognitive impairment. Those with suspected impairment on the TICS-m or proxy instruments were assessed further using the Dementia Questionnaire (DQ) [25]. Those whose DQ indicated possible dementia were assessed in-home by a research nurse and a psychometrician. In-home assessments included an interview to obtain a history of cognitive symptoms and medical history from a knowledgeable informant. The participant completed a standardized neurological examination, neuropsychological testing, blood or buccal DNA collection, and a scripted videotape segment capturing portions of the cognitive status and neurological examinations. The neuropsychological battery included the CERAD battery, Trail Making Test, Parts A and B, Wechsler Memory Scale-Revised Logical Memory I (immediate) and Logical Memory II (delayed), Controlled Oral Word Association, Symbol Digit Modality Test, Finger Tapping Test, Grooved Pegboard Test, and Shipley Vocabulary Test. Final diagnoses were assigned by a consensus panel of neurologists, geriatric psychiatrists, and psychologists after reviewing all information, including relevant medical records. Non-demented cotwins were followed longitudinally at approximately two-year intervals with telephone screening using the TICS-m and DQ. When these interviews suggested the presence of dementia, an in-person clinical assessment was then done. A buccal DNA

sample was collected using a mail-in protocol for non-demented cotwins who did not receive an in-person clinical assessment. In approximately 20% of demented individuals, an in-person evaluation was not possible because the individual refused or was deceased. In these instances, the dementia diagnosis was based on all available data, including telephone interviews, medical records, and neuropathological examination. Dementia was diagnosed based on DSM-III R [26] criteria. Age of onset of dementia was estimated as the age at which the individual unambiguously met DSM-III R criteria based on a systematic review of the chronological history of cognitive and functional decline. These assessment and diagnostic procedures have been successfully used in several other epidemiological studies that require differential diagnosis of dementia, and have resulted in good sensitivity for the detection of dementia and high agreement between clinical and neuropathological diagnoses [27], [29].

Activity Predictors

Participants completed a mail-in questionnaire in 1967 that included items surveying frequency of participation in 13 physical exercise and leisure activities, on a scale of 1 (“never”) to 2 (sometimes), to 5 (“every day”). To be consistent with prior studies, we tallied the number of activities endorsed “sometimes” or more often (2–5).

Total Cognitive Activity was measured by summing frequency of endorsement for nine of the 13 leisure activities. Because active processing is an important component of environmentally enriching activities, we further stratified the nine Cognitive activities using prior scales and ratings to discriminate novel information processing activities, such as “reading”, “studying for courses”, and “extra work” (overtime or other employment) from activities that were more passive or receptive in their processing demands, and did not require a response [2], [4], [30], [31], [32]. These receptive activities included “watching television and listening to radio”, and, “going to movies, theater, art or music”. Cognitive activities judged to be intermediate in their novelty and information processing demands included “home and family activities”, “visiting with friends and relatives”, “club activities” (e.g., parties, card games), and “home hobbies”. Many of these Intermediate Cognitive activities were also social in nature. Endorsement of the four Physical Activities, “outdoor activities”, “sports”, “gardening and home improvement”, and “physical exercise after age 35” were tallied to yield a maximum activity score of 4.

Occupational Demand

Occupational history was collected from a series of questions administered during telephone interviews by trained interviewers, directly from the participant in most cases and from a proxy informant if the participant was unable to complete the interview. Questions included: 1) longest-held job, 2) job title, 3) specific job duties, 4) type of industry, and 5) beginning and ending year for the job. We have previously described our work with these data [33], [9] in which we assigned specific occupational classifications to these responses using the Dictionary of Occupational Titles (DOT), 4th edition [34]. Factor analysis of worker characteristics associated with the DOT-based occupational codes has identified a factor that was interpreted as reflecting the General Intellectual Demands of an individual's job. This factor is similar to occupational complexity factors derived in other research using the DOT. [35, 36]

Statistical Analyses

Mean activity scores for the first affected and unaffected twin-pair groups were compared using a single-tailed t-test under the hypothesis that higher activity would be associated with later dementia onset. Dependent proportional hazard (Cox) ratios were derived by modeling elapsed time from date of leisure activity assessment to either age of dementia or censoring

age, while covarying for age at date of activity assessment. Using dependent models, the risk estimated is the relative difference of midlife activity within the twins, not absolute levels, controlling for genes and many other unidentified factors, which might be assumed more similar for each of the two twins than with any other randomly selected individual. One individual within each twin pair was classified as first affected based on his estimated age of dementia onset relative to the other twin who developed dementia last or remained unaffected. Because of the imprecision in estimating age of dementia onset, discordance between twins required that the unaffected cotwin remain non-demented for at least three years after dementia onset in the first affected twin. Analyses were repeated, stratifying by zygosity and APOE4 allele as a risk modifier among those at elevated genetic risk. Many types of dementia have an extended prodromal period, so we then re-ran the models extending the period of discordance from 3 to 5 years in an attempt to exclude the non-demented cotwins who might have preclinical dementia at the time of the demented twin's onset. Because occupation accounts for a large portion of an adult male's midlife activities, we reran the hazard models using the General Intellectual Demand factor score as a covariate to assess whether this occupational characteristic altered the association between midlife activity and dementia. Individuals within twin pairs were naturally matched on age and the members of a twin pair typically have similar educational backgrounds with 50% of twin pairs in our sample differing in education by one year or less.

Results

Table 1 presents the demographic and medical health characteristics of 147 dementia-discordant twin pairs and shows that they were well matched for education and prevalence of most health conditions that may influence cognition, such as diabetes, hypertension, and myocardial infarction (p 's >0.05), with the exception of stroke. Education levels were high, with many twins obtaining some post-high school education. Over the 15-year follow-up in the Duke Twins Study, 37 of the 147 discordant twin-pair members both developed dementia. Twins were 44.7 years of age, on average, when they completed the activity questionnaire. Those with dementia had a mean age of onset of 72.7 years and the non-demented were 81 years of age at the last follow-up, leading to an average span of 28 – 36 years between midlife activity and the censoring age. We compared the 147 twin pairs included in the present analyses with the 169 pairs that were not included because either one or both members of the pair did not complete the 1967 mail-in questionnaire. Twin pairs completing the questionnaire had more years of education (13.7 vs. 12.8; $p = 0.0005$), however they did not differ in age of dementia onset ($p = 0.43$) or on the censoring age for the non-demented ($p = 0.06$). Activity rates for each item by type (Cognitive or Physical) in Table 2 indicated that the majority of twins were cognitively and physically active, with endorsement exceeding 60% on most items. Twin members who developed dementia first had significantly lower Total Cognitive Activity scores than non-demented twin members ($p=0.004$). The Physical Activity score did not differ between twin members. Frequency of endorsement for each Cognitive and Physical Activity item is presented in Table 2 for the total cohort, and stratified by subsequent dementia status. Item analyses showed that demented twins went less often to the movies, theater, art and music.

Table 3 presents the results of conditional logistic regression models examining whether Total Cognitive and Total Physical Activity scores independently predicted risk for developing dementia first among discordant twin-pairs. Higher Cognitive Activity predicted a significant 26% reduction in risk for developing dementia first (O.R. = 0.74; CI 0.60–0.92). When stratifying by Novel, Intermediate, and Passive/Receptive Cognitive Activity groupings, Passive/Receptive Activity was associated with a 45% reduction in risk for developing dementia first (O.R. = 0.55; CI 0.33–0.92). Differences in Intermediate Cognitive Activity failed to reach significance (O.R. = 0.73; CI 0.51–1.04). When the

analyses were limited to those pairs in which the cotwin remained non-demented for 5 or more years following the onset of the proband, the sample was reduced to 117 pairs, but the results remained similar with the exception that Passive/Receptive Activity results no longer reached standard significance levels (O.R. = 0.57; CI 0.32–1.04). When stratifying twin pairs by zygosity (MZ vs. DZ), in Table 3, Total Cognitive Activity remained a robust predictor, with a 30% risk reduction for dementia onset among MZ twin pairs (N = 84) developing dementia last (O.R. = 0.70; CI 0.53 – 0.91). Within Cognitive Activity groupings, Passive/Receptive Activity fell below significance, and Intermediate Activity attained significance among MZ twin pairs (O.R. = 0.60; CI 0.38 – 0.97; $p < 0.01$). Total Physical Activity did not predict dementia risk reduction among MZ or DZ twin pairs. When occupational factor scores of General Intellectual Demand were added as a covariate to the models, the sample size decreased to 127 pairs due to missing occupation data. Nevertheless, higher Total Cognitive Activity remained associated with lower risk of dementia (O.R. = 0.74; CI 0.58–0.94). In this model, Passive/Receptive Activity was no longer significant (OR=0.70; CI 0.40, 1.22).

APOE4 genotype was available for 80 of the 84 MZ twin pairs. Examination of the protective association of midlife activity among MZ twin pair carriers (1 or 2 APOE4 alleles) and non-carriers (no APOE4 alleles) in Table 4 showed that Total Cognitive Activity was associated with reduced dementia risk only in APOE4 carriers, and not in non-carriers. Despite the small sample size, Total Cognitive Activity was robustly associated with a significant 36% reduction in risk for developing dementia first among APOE4 allele carriers (O.R. = 0.64; CI 0.43 – 0.93). Within Cognitive Activities, this association was more significant for the subset of Intermediate (O.R. = 0.49; CI 0.25–0.95) than for Novel and Passive/Receptive Activities. This association was again restricted to Cognitive Activity and not Physical Activity. None of the interactions between APOE4 and Cognitive Activities were significant (all p values > 0.21).

Discussion

In a 28-year prospective cohort study of twin pairs followed for dementia, greater midlife cognitive activity was protective against dementia onset. Protective effects were most robust in monozygotic twin pairs, where genetic and early-life influences were most tightly controlled. Furthermore, cognitive activity remained protective among monozygotic twin pairs carrying the APOE4 allele, and at elevated genetic risk for AD. When examining these associations by cognitive activity type, intermediate novel activities were most strongly associated with reduced dementia risk. These activities included home hobbies, home and family activities, club activities (e.g., parties, games), and visiting with family and friends, many of which are social in nature. These activities may be indicative of an enriched and novel environment, which has been shown in animal models to enhance synaptic activity and neurogenesis, and promote brain repair [37], [38], [39]. Differences in midlife physical activity did not modify risk. Overall, these findings suggest that an engaged lifestyle in midlife can modify genetic risk in men, and that various activities appear to be protective.

Numerous epidemiologic studies of activity in older adults have observed that novel intellectual, or cognitively stimulating, activities, such as reading, playing mental games and doing crossword puzzles, were associated with reduced dementia risk [3], [2], [14]. These studies have sometimes included other lifestyle activities that have been described elsewhere as “passive” in cognitive demand [30], [32]. We were surprised to observe that these “passive” and receptive cognitive activities, including movie and theater going and television viewing, were associated with reduced dementia risk. This finding is consistent with the use of these items by Wilson and colleagues in their summary measure of cognitive

activity [3], [40], and suggests that they may serve in conjunction with other activities to enrich one's environment and promote neuronal and synaptic efficiency [37], [38].

Many of the intermediate activities (club, visiting with family, friends) and passive (going to movies) activities were social in nature, whereas high cognitive activities surveyed here were primarily solitary (reading, studying). Our intermediate cognitive activity level largely overlaps with a recent definition of “social” or “enterprising” activity in that activities involve “manipulation of others to inform, develop, or cure,” and “to attain organizational or self-interest goals” [41]. A growing body of evidence in middle-aged and older adults suggests that low social activity is associated with increased risk for AD [42], and that mid- and late-life social engagement are associated with better cognitive and physical health, even in the presence of AD pathology [43], [44], [45], [46], [47], [48], [49], [50]. The findings presented here suggest that engaging in activities that incorporate both cognitive and social activity may confer protection, particularly among those at elevated genetic risk for AD. These findings can be integrated with other retrospective studies of midlife activity and dementia risk [51], [52] where greater participation in exchange-of-ideas, and particularly, novelty-seeking activities was associated with decreased odds of AD in late life.

The work presented here builds most directly upon the first published co-twin studies of midlife activity and risk for AD, using similar period activity data (1967) among members of the Swedish Twin Registry [53], [54]. They showed that midlife leisure activity [7] and greater work complexity [8] were each associated with reduced risk for AD in discordant twin-pairs, although the former finding was significant only in women. One interpretation offered by the authors for the null finding in men was that men in midlife may experience more cognitive stimulation through their occupations [55]. Recent data by this group does indeed demonstrate dementia risk reduction among the members of a twin pair with a more cognitively complex occupation [9]. Here, we observed that, beyond occupational demands, midlife leisure activities incorporating voluntary and social behaviors that engage different skills and enrich social networks were protective. Collectively, these results indicate that midlife activity can influence late-life cognitive health in men, as well as women, possibly through enhancement of “cognitive” and “brain” reserves that help to buffer one against the accumulation of brain insults [55], [56].

In this genetically controlled co-twin study, we did not observe a protective association between midlife physical activity and subsequent risk for AD, especially among APOE4 carriers. The literature on physical activity and AD risk is conflicting [57]. Associations between physical activity and AD by APOE4 status are also equivocal [47]. While aggregate physical activity was not protective, one item surveying physical exercise after age 35 may have approached significance if rates had been higher than 42 percent, overall (38% in affected vs. nearly half of last-affected twins). As such, it remains unclear whether the lack of effect for physical activities reflects rigorous control for genetics and early life exposures, limited power, restricted measurement sensitivity or a true null finding that mirrors conflicting findings in the broader epidemiologic literature [14], [15], [16].

These findings provide a life course perspective on dementia risk, and have immediate implications for a generation of male “baby boomers” approaching retirement. Approximately one-third of many individual's lives will be spent post-retirement [58]. The expansion of the human life span makes it imperative to identify those lifestyle opportunities that increase health and “add life to years” [59]. These results can help inform future preventive interventions directed towards health in suggesting that modest increases in the number of cognitively stimulating activities in mid and later ages may yield substantial long-term cognitive health benefits. In particular, those activities associated with dementia risk reduction appear to encompass a range of activities that individuals are likely to maintain

because they are rewarding, entertaining, and engaging. Furthermore, our findings complement those of Karp et al. [50] in suggesting that activities incorporating both cognitive and social activity may confer particular cognitive health advantages over time.

In summary, use of a study design that controlled for genetic and early-life environmental influences and used prospective (midlife) vs. retrospective (late life) activity assessment support the “use it or lose it” hypothesis in aging men. Specifically, participating in a range of cognitively stimulating leisure activities in midlife may delay the onset and reduce risk of dementia in men, particularly among those at elevated genetic risk.

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Table 1

Demographic and health characteristics of twin pairs discordant for dementia onset by 3 or more years.

	Demented First	Demented Last or Absent	p values
N	147	147	
Education (years)	13.9 (3.3)	13.5 (2.9)	0.122
Age Questionnaire Completed	44.7 (3.6)	44.7 (3.4)	0.688
Age at AD Onset, or, Last Follow-up	72.7 (5.6)	76.7 (3.4) 81.0 (3.5)	0.0004
Stroke (%)	34.4	20.3	0.009
Diabetes (%)	16.0	10.7	0.071
Hypertension (%)	43.4	34.9	0.109
Myocardial Infarction (%)	20.8	23.9	0.527

P values for medical conditions based on McNemar's test. Other p-values based on independent t-tests.

Table 2

Mean summed Activity scores and, by frequency of endorsement of each leisure activity item among 147 twin pairs discordant for dementia onset.

Leisure Activity	All (%)	Dementia First (%)	Dementia Last or Absent (%)	t-test p-value
Cognitive		5.8	6.3	0.004**
<u>Novel</u>		2.2	2.3	0.150
Read Newspaper, Magazines, Books		93	96	0.206
Studies	69	65	73	0.144
Extra Work	61	61	61	1.000
<u>Intermediate Novel</u>		3.1	3.2	0.080
Home and Family	99	98	99	0.317
Visit with Friends	95	94	96	0.414
Home Hobbies	71	67	76	0.095
Club Activities	51	50	53	0.505
<u>Passive/Receptive</u>		1.6	1.7	0.016*
Watch Television, Listen to Radio	98	96	99	0.083
Go to Movies, Theater, Art, Music	71	65	77	0.034
Physical		2.8	2.8	0.527
Gardening & Home Improvement	93	93	93	1.000
Outdoor Activities	87	87	88	0.819
Sports	58	56	61	0.317
Physical Exercise After Age 35	42	38	47	0.139

Table 3

Conditional logistic regression models examining risk for dementia for Cognitive and Physical activity scores in discordant twin-pairs.

	All N=147 pairs	Monozygotic N= 84 pairs	Dizygotic N= 63 pairs
Activity Dimension	Odds Ratio (CI)	Odds Ratio (CI)	Odds Ratio (CI)
Cognitive	0.74 (0.60–0.92) **	0.70 (0.53 – 0.91) **	0.84 (0.58 – 1.22)
Novel	0.81 (0.57–1.13)	0.70 (0.46 – 1.08)	1.05 (0.58 – 1.90)
Intermediate	0.73 (0.51–1.04)	0.60 (0.38 – 0.97) **	0.93 (0.52– 1.65)
Passive/Receptive	0.55 (0.33– 0.92) *	0.53 (0.25 – 1.09)	0.55 (0.26 – 1.15)
Physical	0.99 (0.73–1.33)	0.85 (0.56 – 1.29)	1.18 (0.75 – 1.85)

**
p<0.01

*
p < 0.05

Table 4

Conditional logistic regression models examining risk for developing dementia first among monozygotic twin-pairs with (carriers) and without (non-carriers) the APOE4 allele.

	Carriers N= 46 pairs	Non-carriers N= 34 pairs
Activity Grouping	Odds Ratio (CI)	Odds Ratio (CI)
Cognitive	0.64 (0.43 – 0.93) *	0.80 (0.51 – 1.26)
Novel	0.68 (0.38 – 1.2)	0.79 (0.40 – 1.57)
Intermediate	0.49 (0.25 – 0.95) *	0.88 (0.40 – 1.92)
Passive/Receptive	0.46 (0.16 – 1.31)	0.75 (0.26 – 2.22)
Physical	0.82 (0.48 – 1.41)	0.94 (0.48 – 1.87)

*
p <0.05