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The Cache County Study on Memory in Aging: Factors Affecting Risk of Alzheimer's disease and its Progression after Onset

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Abstract

The Cache County Study on Memory in Aging is a longitudinal, population-based study of Alzheimer's disease (AD) and other dementias. Initiated in 1995 and extending to 2013, the study has followed over 5,000 elderly residents of Cache County, Utah (USA) for over twelve years. Achieving a 90% participation rate at enrollment, and spawning two ancillary projects, the study has contributed to the literature on genetic, psychosocial and environmental risk factors for AD, late life cognitive decline, and the clinical progression of dementia after its onset. This paper describes the major study contributions to the literature on AD and dementia.

Introduction

In a joint-report produced by the World Health Organization (WHO) and Alzheimer's Disease International, the world-wide financial costs of dementia in 2010 was estimated at \$604 billion (U.S. dollars) (Alzheimer's Disease International 2012). The personal and societal costs of the condition are expected to skyrocket with the shifting demographics of the world's population. According to a United Nations report, 10% of the world's population was over the age of 59 in the year 2000. Projections indicate this segment will increase to 21% by the year 2050 (United Nations, 2002). Consequently, unprecedented growth in the numbers of persons with dementia is expected over the next several decades. The WHO-AD International report estimated that in 2010, 35.56 million people suffered from dementia. A projected 225% increase suggests that some 115 million people will have dementia by the year 2050 (Alzheimer's Disease International, 2012). AD continues to be the most common form of dementia in late life, but increasingly, it is found to occur with vascular and Lewy body pathology (MRC CFAS, 2001), (Jellinger, 2006). While a cure or means of prevention are lacking, epidemiological studies have identified risk factors that affect the occurrence of

AD and its severity after onset. In this paper, we review the findings of one such study, the Cache County Study on Memory in Aging (USA) and discuss the implications for the risk of AD and its management after onset.

The Cache County Study Population

The Cache County Study on Memory in Aging, was initiated in 1995, with the goal to examine genetic and environmental risk factors of AD and other dementias. Eligible participants were “permanent” residents of Cache County, a rural area located in northeastern Utah, consisting of a population of approximately 70,000 individuals at the study's inception (U.S. Census, 1990). Population attributes included longevity with average life expectancy exceeding national averages (Murray et al. 1998), relatively high levels of educational attainment, lifestyle characteristics with an emphasis on physical activity, and a relatively stable population fostered by a close-knit community (see Hayden and Welsh-Bohmer, 2012 for discussion (Hayden & Welsh-Bohmer, 2012)). The study enrolled 90% of the county's residents age 65 years and older. The sample was 99% Caucasian, 58% female, and ranged in age from 65 – 105 years, with a mean (SD) of 75.9 (7.3) years at enrollment. Range of formal education was 0 – 20 years, with a mean (SD) of 13.1 (2.9) years (Tschanz et al., 2005). Four triennial waves of dementia ascertainment identified 942 persons with dementia over the course of 12 years, 58% with Possible/Probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, 13% with Vascular Dementia according to National Institute of Neurological Disorders and Stroke and Association-Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria, 11% AD comorbid with other forms of dementia, and 18% with other dementias or an indeterminate cause. Persons with dementia and their caregivers were also followed longitudinally for up to 9.5 years. Discussed below, the project has examined the role of genes, health conditions, lifestyle, and psychosocial factors on dementia risk and their effects on the expression of dementia after onset.

Do prevalence and incidence rates of AD continue to rise throughout the lifespan?

Owing to the relatively large numbers (14%) of participants over the age of 84 in the Cache County Study (Tschanz et al., 2005), the study had a unique opportunity to examine the risk of dementia in extreme old age. The prevalence of AD in the 5092 baseline participants was estimated at 6.5% and all-cause dementia at 9.6%, with genotype at the Apolipoprotein E (APOE) locus affecting the age of onset. Higher proportions of women than men developed AD if they were APOE E4 carriers (Breitner & Miech, 2000). Three-year incidence rates showed substantially higher rates among women than men after age 85 (Miech et al., 2002). While both prevalence and incidence of AD rose exponentially with increasing age, subsequent declines were observed, the age of which varied by sex and APOE genotype. Thus, the incidence of AD among men homozygous for APOE E4 peaked at approximately age 80 and among women at approximately age 84 before declining, whereas peak incidence for APOE E4 heterozygotes was approximately age 90 for men and age 95 for women. Peak incidence for noncarriers of the APOE E4 allele occurred at approximately age 93 for men and age 97 for women (Miech et al., 2002) before declining. An analysis of lifetime incidence in the Cache County population suggested that some 28% of individuals surviving

to late old age may not be susceptible to developing AD, mostly among noncarriers of the APOE E4 allele (Khachaturian et al. 2004).

The results from Cache County are similar to those observed in other populations where higher risks were observed among APOE E4 carriers (Farrer et al., 1997); (Plassman et al., 2007). Unlike other studies, years of educational attainment was not a predictor of AD incidence in Cache County, possibly reflecting population homogeneity on this attribute and low representation among those with less than a high school degree. A finding in Cache County but less consistently reported in the literature was the elevated risk among women (Gao et al. 1998); (Ruitenberg et al. 2001); (Plassman et al., 2007), which generally appears in the oldest segments of populations (Ruitenberg et al., 2001) however, see (Corrada et al. 2010). Although most population studies show a continual rise in the rates of AD or dementia with increasing age, many report a slowing in the rate of increase in extreme old age (after age 90; (Ruitenberg et al., 2001), (Hall et al., 2005)), and the Cache County Study shows a decline. Interestingly, the 90+ Study, consisting of a population of 1150 nonagenarians and centenarians from a retirement community in southern California reported a continued increase in the incidence rates of dementia with age (Corrada et al., 2010). In this study, the overall incidence rate was 18.2% per year, with an exponential increase from age 90-94 at 12.7% to 40.7% among centenarians. Despite these rising rates, the literature on nonagenarians and centenarians reports a significant proportion do not develop dementia (Andersen-Ranberg et al. 2001) (C. H. Kawas & Corrada, 2006); however, whether the actual risk of dementia in extreme old age declines remains controversial. Differences among study results may reflect in part, the challenges in studying the rates of dementia incidence in the upper extremes of the lifespan including diminishing sample sizes and difficulties diagnosing dementia in the context of age-related changes in cognition and higher rates of medical comorbidities which may confound causes of cognitive impairment (Slavin et al. 2013).

How common are milder forms of cognitive impairment in late life?

Estimates of milder forms of cognitive impairment such as “Cognitive Impairment no Dementia” (CIND) and prodromal AD were reported in two waves of the Cache County Study. In Wave 1, crude prevalence of any type of mild cognitive impairment in the baseline 5092 population was 4%. Prodromal AD made up 1.6% of the population (Tschanz et al., 2006). These values are substantially lower than estimates from other populations. For example, the Canadian Study on Health and Aging, which first introduced the term, “Cognitive Impairment No Dementia” reported a prevalence of 16.8% of CIND among their sample of persons aged 65 years and over (Graham et al., 1997). The relatively low rates identified in the first wave of the Cache County Study likely reflected the multi-stage screening and assessment protocol that was designed to identify cases of dementia rather than milder forms of cognitive impairment. Three-year conversion rate to dementia in Cache County was 54.9% for those with prodromal AD (Tschanz et al., 2006), which was defined as a history of functional impairment consistent with a CDR of 0.5 and/or objective assessment of mild impairment in cognition suggestive of early-stage AD that were not attributable to other medical or health conditions (Breitner, Welsh, et al. 1995; Hayden & Welsh-Bohmer, 2012). Approximately 39.1% (or annual rate of 14%) of those with other

forms of cognitive impairment or CIND converted to dementia. The majority of the converters in both prodromal AD and CIND developed AD (Tschanz et al., 2006). The conversion rate in Cache County exceeded that observed in the Canadian Study, which reported a 47% conversion to dementia over five years (9.4% annually; (Tuokko et al., 2003)), and probably reflects the more severe cases of cognitive impairment identified in the former. The Cardiovascular Health Study (CHS) reported that 51% of their Mild cognitive Impairment (MCI) sample converted to dementia over a mean follow-up of 4.3 years (approximately 12% annually; (Lopez et al., 2007)). Among very old individuals in the 90+ Study, the annual dementia incidence rate varied by MCI subtype: amnesic MCI was nearly 40% per year and nonamnesic MCI was 14% per year (Peltz et al. 2011).

Notably, several studies report significant “reversion” to “normal” among groups of CIND or MCI. The CHS reported 18% of their MCI sample reverted to “normal” status. The Personnes Agées QUID (PAQUID) Study reported an approximate 40% reversion rate (Larrieu et al., 2002), and the Monongahela (Pennsylvania, USA) Study reported a 10-27% annual reversion rate to a Clinical Dementia Rating (CDR) of 0, depending on the definition of MCI (Ganguli et al., 2011). In Cache County, 26% of the prodromal AD and 36% of those with CIND reverted to “no impairment” or a screen negative designation over a three-year interval. Variations in diagnostic criteria for MCI and CIND, study design and population attributes likely underlie differences in the prevalence figures of MCI/CIND and rates of conversion (to dementia) or reversion to a less cognitively impaired status. Clinic-based samples of MCI patients generally show higher rates of dementia incidence than population-based samples (Mitchell & Shiri-Feshki, 2009).

In Wave 3 of the Cache County Study, in which more sensitive screening methods were employed to identify various types of cognitive impairment, crude prevalence of CIND constituted 21% of the surviving population, then numbering 2324 and of a minimum age of 72. Approximately 8% had a diagnosis of prodromal AD or amnesic MCI. Prevalence of CIND increased with age and presence of the APOE E4 allele. Neuropsychiatric symptoms were more common among those with CIND compared to those without cognitive impairment (Peters et al. 2012). Conversion rates from CIND to dementia was 12% annually, similar to the rate observed in the prevalence and first incidence wave of Cache County. Presence of neuropsychiatric symptoms increased the risk of conversion to dementia at follow-up, even while controlling for age, APOE genotype and degree of cognitive impairment (Peters et al. 2013). Greater severity of medical comorbidity among persons with CIND is associated with worse cognitive and functional abilities (Lyketsos et al., 2005) and may also contribute to increased risk of dementia. Limitations in daily living activities also may reflect imminent dementia in the broader population (Fauth et al., 2013).

Modifiable risk factors for AD and cognitive decline in late life

Perhaps the most studied topic in the Cache County Study has been of modifiable factors that may affect the risk of AD, dementia and cognitive decline. Medical or health conditions, diet and dietary supplements, pharmacological exposures, and life events significantly predict risk of AD or rate of cognitive decline.

Vascular risk factors including hypertension, high cholesterol, diabetes, and atherosclerosis are well known in the literature to increase risk of AD, with estimated effects ranging from 1.2 to 4 times, depending on the risk factor in question (Kivipelto et al. 2001), (Launer et al. 2000), (Luchsinger et al. 2005), (Whitmer et al. 2005), (Ott et al. 1999), (Notkola et al. 1998), (Reitz et al. 2007), (Hofman et al. 1997). Obesity, usually indicated by a body mass index (BMI) ≥ 30 or some anthropomorphic indicators such as waist circumference, has been associated with a 2- to 5-fold increase in risk of AD (see review by Gustafson (Gustafson, 2008)). In the Cache County Study, the role of vascular risk factors in predicting three-year conversion rates to AD varied by sex and the specific risk factor in question. Obesity at baseline, defined as BMI ≥ 30 , increased the risk of AD in women by a factor of 2 in comparison to non-obese men, whereas among men, diabetes showed a slight, though non-significant increase in the risk of AD (Hayden et al., 2006). In contrast to the other studies referenced above, neither a history of hypertension nor high cholesterol (disregarding any medication treatments) increased the risk of AD in Cache County and in fact, a history of high cholesterol was associated with a 53% reduction in risk. Divergence in study results may reflect the age of onset of these risk factors (not examined in Cache County) as most studies report increased risk with onsets in midlife (Notkola et al., 1998), (Kivipelto et al., 2001). Furthermore, treatment of these conditions was quite high in the Cache County population, for example 86% of those with hypertension reported use of antihypertensive medications (Hayden et al., 2006). This is notable in light of the lower rates of AD incidence with use of these medications in this cohort (see below; (Khachaturian et al., 2006)).

Do common medications or dietary supplements modify the risk of AD and cognitive decline?

Several analyses undertaken in the Cache County Study examined whether consistent use of various medications or dietary supplements altered the risk of AD or the rate of cognitive decline. The effects of non-steroidal anti-inflammatory medications (NSAIDs), anti-hypertensive medications, “statin” medications, hormone therapy (HT), dietary intake and nutritional supplements have been examined. There is evidence of a reduction in AD risk or the rate of cognitive decline associated with use of NSAIDs, HT, and anti-hypertensive medications as well as a varied diet consisting of recommended nutrient groups, and greater intake of dietary and supplemental use of antioxidant vitamins E and C.

NSAIDs

Along with a number of other observational studies, the Cache County Study reported a reduction in AD risk for consistent users of NSAIDs in cross-sectional (prevalence wave) and longitudinal analyses. The cross-sectional analyses reported a 50 - 83% reduction in risk of AD for various combinations of non-aspirin and aspirin NSAIDs (Anthony et al., 2000). Subsequent work by Zandi and colleagues (Zandi et al. 2002a) in the first incidence wave found a 55% reduction in the risk of AD if NSAID use extended for more than two years duration; little to no advantage was observed for those reporting shorter duration use. Interestingly, in analyses extending the period of observation to Wave 3, age of use and APOE E4 genotype modified the association between NSAID intake and *cognitive trajectories*. Persons initiating NSAIDs after the age of 65 (the mean age of use in this

cohort) had higher cognitive test scores at baseline on the Modified Mini-Mental State Exam (3MS) compared to non-users, whereas those initiating use before age 65 scored similarly to non-users, but declined more slowly. The beneficial association of NSAIDs was observed only among APOE E4 carriers, who showed both higher cognitive test scores at baseline and slower rates of decline over time if taking NSAIDs. There was no effect of NSAID use among APOE E4 noncarriers (Hayden et al., 2007). Notably, interactions of NSAID use and APOE genotype were not significant when examining risk of AD (Anthony et al., 2000), (Zandi et al. 2002a).

Although the analyses in Cache County suggest a protective effect for NSAIDs at least among a subgroup of individuals, these results are inconsistent with those of randomized controlled trials for the treatment of AD (Aisen et al. 2002), (Aisen et al. 2003), (Reines et al. 2004), (Scharf et al. 1999), (Soininen et al. 2007) or its prevention (Adapt Research Group et al., 2007), (ADAPT Research Group, 2006), (Martin et al., 2008). Furthermore, at least one community-based, observational study reported an *increase* in AD risk with the use of NSAIDs, the difference in this study's results from other observational studies attributable possibly to the older age of the cohort (Breitner et al., 2009). It is difficult to reconcile the divergent effects of NSAID use between those reported from observational studies and randomized controlled trials. Some of the aforementioned effect modifiers such as age and duration of use and APOE genotype may hold some clues (Hayden et al., 2007), (Yip et al. 2005).

Hormone therapy in the Cache County Study: Do duration and type matter?

Research on HT use in the Cache County cohort suggests some variability of effects based on factors such as duration of use and possibly the type of HT. First examined in relation to cognitive impairment in the baseline population, past and current users of HT scored higher on a cognitive screening test, the 3MS (Steffens et al., 1999). This was followed by a report of reduced rate of cognitive decline among “ever” users of HT over a three-year interval (Wave 1 to Wave 2), with greatest effects observed among those age 85 years and older (Carlson et al., 2001). Analyses using the first incidence wave data, found that the risk of AD was reduced by 41% among women who ever used HT compared to women who never used the medications. When compared to men, risk of AD among women was greater after the age of 80, but with ten years duration of HT use, the risk of AD in women no longer differed from that of men. The beneficial effects of HT were found among former users, with no effect among current users of less than 10 years duration (Zandi et al. 2002b). These results held after controlling for multivitamin and calcium use, indicators of health-conscious behaviors employed in previous analyses (Carlson et al., 2001).

The beneficial effects of HT are consistent with some (Kawas et al., 1997), (Tang et al., 1996) but not all observational studies (Brenner et al., 1994), (Seshadri et al., 2001). Again, the results of randomized controlled trials suggested no benefit in the majority of treatment trials of AD (Henderson et al., 2000), (Mulnard et al., 2000), (Resnick & Henderson, 2002), however see (Asthana et al., 2001). The large, randomized controlled prevention trial undertaken by the Women's Health Initiative further reported no benefit in the study that was discontinued early due to adverse events in the treatment arms. Rather than any hint of

benefit, analyses of trial data raised the possibility of harmful effects, at least with respect to an increased rate of cognitive decline and higher incidence of all-cause dementia in the estrogen and progestin treatment group (Rapp et al., 2003), (Shumaker et al., 2003) or overall when pooling treatment groups (Shumaker et al., 2004). The adverse events observed in this clinical trial led to the issuance of a “black box” warning by the Federal Drug Administration for estrogen compounds (Federal Drug Administration, 2003).

Attempts to reconcile observational study results with those of randomized trials led to hypotheses that the *timing and duration* of HT use may be critical factors in determining their effects on cognition and AD risk. As noted above in the Cache County Study results, any beneficial effect of HT was restricted to women with prior and longer duration use. Moreover, in Cache County, a two-fold *increase* in risk of dementia was observed among HT users within three or between three to ten years of the study's baseline (Breitner & Zandi, 2003). Additionally, *type* of estrogen preparation may influence its effects. For example, the combination of estrogen plus progestin (combined equine estrogen (CEE) with medroxyprogesterone acetate; MPA) may not incur beneficial effects of estrogen alone as MPA reportedly neutralizes any neuroprotective effects of estrogen (Brinton & Nilsen, 2003). A subsequent observational study using medical and pharmacy records from a health maintenance organization in California found that women taking HT at midlife (mean age 48) had a 26% reduction in the risk of dementia whereas those taking HT in late-life had a 48% *increase* in risk compared to women never treated with HT (Whitmer et al. 2011). Recent analyses conducted in Cache County, extending now to 11 years of observation from all four study waves, found that women who used any form of HT within five years of menopause was associated with a 30% reduction in the risk of AD, particularly when taken for a duration of ten or more years. No reduction in risk was observed among those initiating treatment five or more years after menopause. Notably, an increased, though statistically nonsignificant risk was observed for those using estrogen-progestin preparations within three years of the baseline assessment (Shao et al., 2012). Thus, the data from Cache County supports the hypothesis that the timing, duration and possibly type of HT can affect the risk of AD later in life.

Other Medications

Among other commonly prescribed medications studied in the Cache County Study were those used to treat high cholesterol and hypertension. Despite promising reports from some studies (Jick et al. 2000), (Wolozin et al. 2000), (Rockwood et al. 2002), (Hajjar et al. 2002), a number of studies including Cache County (Zandi et al., 2005) found no reduction in AD risk for users of lipid lowering agents such as 3-hydroxymethyl-glutaryl-CoA reductase inhibitors (or “statins”) (Li et al., 2004), (Rea et al., 2005). Randomized controlled trials have also shown no benefit in reducing cognitive decline with statin medications (Santanello et al., 1997), (Shepherd et al., 2002). By contrast, use of any antihypertensive medication was associated with a 36% reduction in AD risk in Cache County. The greatest reduction in risk was found for use of a potassium sparing diuretic, which was associated with an 84% reduction (Khachaturian et al., 2006). The results of randomized controlled trials are mixed for antihypertensive medications (e.g., (Peters et al. 2008), (Bosch et al. 2002), (Tzourio et al. 2003), (Forette et al. 1998), (Forette et al. 2002)) and may differ by type of compound

(Shah et al. 2009). Beneficial effects of antihypertensive medications may in part be due to reduced occurrence of stroke (e.g., (Bosch et al. 2002), (Tzourio et al. 2003)). In the Cache County Study, statin and antihypertensive medications have also been examined in relation to the rate of dementia progression *after* the onset of AD (see below).

Diet, dietary supplements, lifestyle factors and life events

The Cache County Study has identified a number of lifestyle factors and life events that modify the risk of cognitive decline and dementia in late life. A varied diet rich in fruits, vegetables, lean meats, fish, low-fat dairy products, and whole grains (per recommended dietary guidelines) was associated with higher cognitive scores over 11 years of observation in the Cache County Study (Wengreen et al. 2009). Those with the highest scores of recommended foods declined by an average of 3.4 points on the Modified Mini-Mental State Exam (3MS) compared with the lowest group, which showed an average decline of 5.2 points over the 11 years. However, statistical models testing differences in *rate* of decline were not significant. Antioxidant vitamins are associated with a slower rate of cognitive decline and lowered risk of AD. Higher intake of vitamin C alone or with vitamin E (from food sources) was associated with higher cognitive 3MS scores at baseline. Overall, greater intake of vitamins C and E and carotene was associated with a slower rate of 3MS decline over the 11-year study interval (Wengreen et al. 2007), and use of vitamin E in combination with vitamin C supplements was associated with lower prevalence and three-year incidence of AD (Zandi et al. 2004). In separate analyses focusing on B vitamins, no significant effects were found for dietary folate, vitamin B-12, or vitamin B-6 on the risk of AD (Nelson et al. 2009).

The Cache County Study results of diet, nutritional supplements and lifestyle factors are consistent with other studies reporting beneficial effects of dietary factors such as fish consumption (Morris et al. 2003), (Morris et al. 2005), a Mediterranean style diet (Scarmeas et al. 2006), and antioxidant vitamins (Morris et al. 1998), although negative findings have also been reported (Luchsinger et al. 2003). A few randomized controlled trials (RCT) have examined the effects of dietary supplements. An RCT of vitamin E found no benefit in delaying the onset of AD in those with MCI (Petersen et al. 2005), and another reported no benefit of docosahexaenoic acid in AD (Quinn et al.). It is possible that results reporting a beneficial effect of diet and dietary supplements are due to the operation of other factors such as an overall healthy lifestyle. Thus, Norton et al. (Norton et al. 2012) expanded the analyses of dietary patterns in Cache County to additional lifestyle behavior patterns. Examined were diet (that which most closely followed the “Dietary Approaches to Stop Hypertension or DASH diet), physical activity, church attendance, social interaction, alcohol use, and smoking. Among four lifestyle patterns, those that had “healthy” aspects to the behavior patterns were associated with reduced risk of AD and all-cause dementia.

Do life events associated with psychosocial stress affect cognitive decline and risk of AD?

The Lifespan Stressors and AD Study, an ancillary project to the Cache County Study, examined the association of psychosocial stress and risk of dementia and rate of cognitive decline in late life. Life events such as early parental death and late-life stressful events were associated with worse cognitive outcomes. In cross-sectional analyses, death of a father

during childhood was associated with a 3-fold increase in risk of all-cause dementia (Norton et al. 2009a). Using death certificate data for determining relatives' deaths and incorporating data from all four study waves, there was an increased risk of AD for mother's death during a participant's adolescence and father's death during his/her childhood. Interestingly, the associations were no longer apparent with parental remarriage (Norton et al. 2011). The non-normative event of death of a child in early adulthood was associated with a one-point per year faster rate of cognitive decline over the eleven-year follow-up interval. However, the results were found only among carriers of the APOE E4 allele, and subsequent births decreased the magnitude of cognitive decline (Greene et al. In press).

Among late-life psychosocial stressors, the Cache County Study reported elevated incidence rates for dementia among spouses of persons with dementia with a 1.6-fold increase in risk of dementia among those exposed (Norton et al., in press). Although one may speculate the psychological stress and burden associated with providing care for a spouse with dementia underlies the increased risk, common exposures over the years of marriage and shared residence may provide alternative explanations (Norton et al. 2010). Regarding cognitive decline, an examination of late-life psychosocial stressors revealed a more rapid rate of decline among persons with a higher number of stressful life events and those with fewer years of education (Tschanz et al. 2013a). These results raise the possibility of a beneficial effect of cognitive reserve or more favorable socioeconomic factors typically found among those with more years of formal education that may mitigate deleterious effects of psychosocial stress on cognition. Generally, the results of psychosocial stressors on cognitive decline and risk of dementia are broadly consistent with other studies reporting a disadvantage for those experiencing stressful life events across the lifespan (Persson & Skoog 1996) or other early life factors (Moceri et al. 2000), (Borenstein et al. 2005), (Moceri et al. 2001).

Factors affecting the course of AD after the onset of dementia

With four waves of dementia ascertainment from the Cache County Study, an ancillary project, The Cache County Dementia Progression Study (DPS) was in a unique position to study persons with new onset of dementia (incident cases) and examine the clinical progression of dementia in three domains: cognition, function and neuropsychiatric symptoms (NPS). The study followed Cache County Study participants with dementia for up to 12 years after the onset of dementia. With high participation rates (over 95% at follow-up), the majority of the sample participated until their deaths. Prior to the DPS, much of the literature on factors affecting the rate dementia progression was based on clinical samples, which in general are notable for consisting of younger, more highly educated individuals of higher socioeconomic status (Barnhart et al. 1997) and presumably more severe disease symptoms. Discussed below, the DPS identified a number of participant (medical, sociodemographic) and caregiver factors that were associated with the rate of dementia progression.

Variability in the course of AD

One of the goals of the DPS was to carefully estimate the rate of dementia progression among persons with AD. Similar to reports from other studies (Behl et al. 2005), (Mortimer

et al. 1992), (Swanwick et al. 1998), (Schmeidler et al. 1998), the DPS reported highly variable rates of cognitive and functional decline in AD (Tschanz et al. 2011). The mean rate of decline on a commonly used cognitive test, the Mini-Mental State Exam (MMSE) was 1.5 points per year, considerably lower than the annual rate of change of 3 points reported in most studies (Behl et al. 2005). While all three domains were characterized by substantial variability among participants with AD, the NPS trajectory showed the greatest variability (numerous peaks and valleys) within persons over the course of dementia. Furthermore, examining rates of decline in each of the cognitive, functional and NPS trajectories indicated that 30-58% of the sample could be described as “slow” decliners, that is participants who exhibited a decline of no more than one point per year on the measures in each domain (Tschanz et al. 2011). Women and persons with younger onset ages declined faster in the cognitive domain. Notably, APOE genotype or years of education did not affect the rate of progression in any of the three domains. Other studies have reported mixed results for both risk factors (Aguero-Torres et al. 1998b), (Bowler et al. 1998), (Adak et al. 2004), (Stern et al. 1999), (Aguero-Torres et al. 1998a), (Swanwick et al. 1998). With respect to severe disability, DPS found that about 25% of persons with AD ever progress to severe dementia, the majority dying prior to this point (Rabins et al. 2013). If researchers can identify modifiable factors that slow the rate of progression, enormous economic savings, reduced caregiver burden and higher patient quality of life may be achieved. The DPS has identified several factors that may lead to strategies to slow the progression of AD.

Modifiable person-factors affecting dementia progression

The DPS has identified a number of health-related factors that affect rate of dementia progression. Thus participants with AD and a history of atrial fibrillation, systolic hypertension and angina were each associated with more rapid cognitive (0.45 – 1.78 points/year) and functional (0.50 - 1.80 points/year) decline on the MMSE and Clinical Dementia Rating (CDR)-sum of boxes, respectively. Among older participants, there was even more rapid decline for those with a history of systolic hypertension, angina and myocardial infarction (Mielke et al. 2007) and myocardial infarction was associated with more rapid functional decline among APOE E4 carriers (Mielke et al. 2012b). Overall health was also an important predictor of cognitive and functional trajectories in AD. Persons with unstable or poorly controlled health conditions scored approximately 1 point worse on the MMSE and 1.78 points worse on the CDR-sum of boxes over the course of dementia (Leoutsakos et al. 2012).

Among various treatments, DPS reported slower rates of cognitive and functional decline in AD for several medical treatments. Thus, history of coronary artery bypass graft (CABG), anti-hypertensive (Mielke et al. 2007), (Rosenberg et al. 2008), and statin medications (Rosenberg et al. 2008) were associated with slower progression. History of CABG was associated with an approximately 1.5 points/year slower decline on the MMSE and CDR-sum of boxes (Mielke et al. 2007). The use of statin and beta blocker (anti-hypertensive) medications was associated with slower functional decline of 0.75 and 0.68 points/year, respectively. Diuretic use was associated with a nearly 1.0 point/year faster decline on the CDR-sum of boxes (Rosenberg et al. 2008). The use of dementia medications such as cholinesterase inhibitors or memantine, taken by approximately 22% of the cohort was

associated with higher baseline cognitive scores, but did not affect rate of decline (Tschanz et al. 2011). However, in more refined analyses, greater duration of treatment with a cholinesterase inhibitor was associated with slower cognitive and functional decline among women APOE E4 carriers, but faster progression in men (Mielke et al. 2012a). An examination of the effects of psychotropic medications was generally associated with worse cognitive, functional and NPS trajectories, indicating persons with more severe disease more often received these treatments (Rosenberg et al. 2012). In summary, various vascular treatments and the use of cholinesterase inhibitors were associated with reduced rates of dementia progression in persons with AD, but some of the effects may be modified by medication type, sex and APOE genotype.

Factors associated with neuropsychiatric symptoms

As noted above, the course of NPS in AD is marked by significant fluctuations in the presence and severity of symptoms over time. The prevalence of each symptom varied by symptom type. Extremely rare was elation at 1% and most common was depression at 29% early in the course of dementia. Overtime, the prevalence of each symptom increased, the most common of which were depression and apathy (Steinberg et al. 2008), (Tschanz et al. 2011). Although fluctuating in severity over time, NPS were quite persistent in that 81% of persons with NPS at baseline also showed at least one symptom over an 18-month interval (Steinberg et al. 2004). Consistent with other studies (e.g., (Frisoni et al. 1999), (Aalten et al. 2003), (Garre-Olmo et al. 2010)), there is significant co-occurrence of NPS symptoms. Among the three classes of AD participants in Cache County identified by NPS patterns, the largest class consisted of those with none or a single NPS, a second class consisted of affective symptoms (depression, irritability, and anxiety) and a third consisted of psychotic symptoms (Lyketsos et al. 2001).

Few risk factors have been identified for increasing NPS in AD, but in cross-sectional analyses, DPS reported that a history of stroke showed an approximate 4-fold increased risk for depression, apathy and delusions, and history of hypertension was associated with a 2-fold increased risk of delusions, a 4-fold increased risk of anxiety and a 3-fold increased risk of agitation (Treiber et al. 2008). However, in recent longitudinal work examining vascular risk factors and conditions, only a history of antihypertensive medication use was associated with a modest increase in total NPS scores (across 10 domains on the UCLA Neuropsychiatric Inventory) and an increase in affective symptoms (Steinberg et al. 2013). Clearly, greater understanding of the fluctuating nature of individual NPS and symptom clusters is needed over the course of AD. Identifying modifiable factors that may provoke their occurrence may lead to effective strategies for management, an important goal given the significant burden associated with NPS and the limited treatment options available (Lyketsos et al. 2011).

Do factors in the care environment affect the rate of dementia progression?

Although the effects of caregiving and the associated stress or burden have been well-studied in relation to caregiver outcomes, few investigations have examined factors in the care environment (including caregiver characteristics) in relation to outcomes for persons with dementia. DPS has reported significant effects of the care environment on the rate of

decline in AD and all-cause dementia. For example, participant engagement in more cognitively stimulating activities was associated with slower cognitive decline early in the course of AD (Treiber et al. 2011), and a closer caregiver and care-recipient relationship was associated with slower cognitive and functional decline (Norton et al. 2009b). In the latter analysis, caregiver-care recipient dyads with closer relationships showed approximately 0.7 – 1 point per year slower decline on the MMSE. Recent work found that the caregiver personality trait of neuroticism was associated with faster cognitive decline among AD participants cared for by an adult child and slower decline among AD participants cared for by an adult child with higher extraversion scores (Norton et al. In Press.). In other analyses examining participants with all forms of dementia, those whose caregivers reported “regular” use of coping strategies characterized by a problem-focused or problem solving approach showed an approximate 2-point per year slower rate of cognitive decline on the MMSE and a 1.65 slower rate of functional decline on the CDR-sum of boxes than care recipients whose caregivers reported never using this strategy (Tschanz et al. 2013b). Overall, results from the DPS suggest that aspects of the care environment may hold important means to influence the clinical course of individuals with dementia. Additionally, some of the caregiver factors that appear to benefit the care recipient may have positive effects for the caregiver (Piercy et al. 2012), although potential negative effects have also been observed (Fauth et al. 2012).

In summary, since 1995, the Cache County Study and spinoff initiatives have contributed to the epidemiological literature of Alzheimer's disease, late-life cognitive decline, and the rate of clinical progression after the onset of dementia. Building on past work and with new collaborations, the Cache County Study joins a number of other large cohort studies to increase our understanding of the genetic and environmental factors that modify the risk for dementia in late-life. Results demonstrate cognitive effects of both biological (e.g. medications and nutrient and dietary intake) and psychosocial (e.g. early parental death, offspring death) exposures. These findings may inform future preventive and therapeutic interventions but also help to identify subpopulations more vulnerable to AD. Study investigators continue to work to identify factors that may ultimately lead to the prevention of AD, delay its onset, or ameliorate its severity over the course of dementia.

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