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OVERVIEW AND FINDINGS FROM THE RELIGIOUS ORDERS STUDY

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Abstract

The Religious Orders Study is a longitudinal clinical-pathologic cohort study of aging and Alzheimer's disease (AD). In this manuscript, we summarize the study methods including the study design and describe the clinical evaluation, assessment of risk factors, collection of ante-mortem biological specimens, brain autopsy and collection of selected post-mortem data. The results: 1) review the relation of neuropathologic indices to clinical diagnoses and cognition proximate to death; 2) examine the relation of risk factors to clinical outcomes; 3) examine the relation of risk factors to measures of neuropathology; and 4) summarize additional study findings. We then discuss and contextualize the study findings.

Keywords

Religious Orders Study; Dementia; Alzheimer's Disease; Cognitive Function; Epidemiology; Clinical-pathologic Study; Neuropathology; Cohort

INTRODUCTION

Careful clinical characterization followed by examination of neural tissues after death has been a fundamental approach to understanding neurologic diseases for more than two centuries. For much of the 19th century, post-mortem examination was limited to macroscopic evaluation. However, developments in optics, tissue fixation, and tissue staining ushered in the modern era of histopathologic examination. In the first decade of the 20th century, Professor Alzheimer combined the case report of a woman with progressive dementia with microscopic histopathologic examination of her brain and described the disease that currently bears his name [1]. For the next several decades, AD was considered a relatively rare progressive dementia of mid-life and was thought to be something quite distinct from the senility of old age. A series of clinical-pathologic studies in the late 1960's, however, demonstrated that old age dementia was often associated with the same lesions described by Dr. Alzheimer and that AD was likely the most common cause of dementia in old age [2–5], and even present in brains of persons without dementia [4]. Within a few years, the significance of this observation was brought into focus in an editorial forecasting the increasing burden of AD associated with the aging population [6]. Recognition of the

impending public health problem contributed to the formation of the Neurobiology of Aging Program within the nascent National Institute on Aging and the emergence of the AD Centers program. By the mid 1980s, consensus criteria for the clinical [7] and pathologic [8] diagnoses of AD were established, and standardized clinical and pathologic procedures were developed and being implemented nationwide [9–10]. The concept of definite AD as a clinical pathologic entity with progressive dementia documented during life and neocortical plaques and tangles documented at autopsy was solidified.

AD centers across the country became expert at enrolling subjects with typical AD and following them until death and obtaining brain autopsy [11–15]. However, the standard approach to obtaining specimens from persons without AD was to monitor the autopsy suite for brains from older persons, document the absence of AD pathology, and subsequently review medical records to ensure the absence of clinical evidence of obvious dementia [16–19]. Obtaining brain autopsies from persons without dementia clinically evaluated proximate to death was problematic. For example, between 1987 and 1995, the Consortium to Establish a Registry for AD (CERAD) which included 24 federally funded AD Centers from across the United States enrolled 1094 patients with AD and 463 controls into a longitudinal study of aging and AD that included brain donation. During this time period there were 202 autopsies out of 411 deaths among those with AD; by contrast, there were only 8 autopsies out of 25 deaths among those recruited without dementia [20]. Prior to 1993, there were very few reports of neuropathologic findings among persons prospectively evaluated and documented to be free of dementia proximate to death [21–23]. None of these studies included more than 20 persons without dementia. At that time, carefully examined clinical-pathologic single case studies of non-demented elderly were of interest [24]. In spite of these small numbers, it became evident that some older persons without dementia could have widespread AD pathology. This finding challenged the idea that there was a simple correspondence between the dichotomous clinical and pathologic diagnoses of AD. Thus, by the early 1990's there was an emerging consensus that more information was needed regarding the neuropathologic changes associated with aging among persons without dementia.

In early 1992, we learned of a fascinating study being conducted by Drs. David Snowdon, Jim Mortimer, Bill Markesbery and colleagues with the School Sisters of Notre Dame [25]. The Nun Study was following several hundred sisters over age the age of 75 years, most of them without dementia, all of whom volunteered to brain donation at death. The organ donation effort was embedded within a well-conceived epidemiologic birth-cohort study. Building on the success of Nun Study, we approached a number of Religious communities to obtain support for the Rush Religious Orders Study. The proposal was submitted to the National Institute on Aging for funding as a Core of the Rush Alzheimer's Disease Core Center in October 1992. It was funded in July 1993 and clinical evaluations commenced in January of 1994.

The Religious Orders Study had two overall goals intended to complement other ongoing work in the field, especially the Nun Study. One was to provide a source of brain tissue from well characterized comparable men and women with and without dementia for clinical-pathologic studies of aging and AD. The second was to obtain brain tissue from persons on whom risk factor information was obtained prior to the onset of dementia for studies linking risk factors to clinical and neuropathologic phenotypes. To accomplish these goals, the study enrolled participants without dementia and documented a wide range of potential risk factors for common chronic conditions of old age. Thus, the Religious Orders Study has all of the essential features of a cohort study of risk factors for incident AD and cognitive decline. In addition, all participants must agree to organ donation as a condition of entry. Over time,

some participants develop dementia prior to death resulting in post-mortem material from comparable men and women with and without dementia.

METHODS

Study Design

The Religious Orders Study enrolls Catholic nuns, priests and brothers, from more than 40 groups across the United States (Figure 1). Participants are without known dementia and agree to annual clinical evaluation and brain donation (some in the Chicago area also agree to donate, spinal cord, nerve, and muscle). Each subject signs a consent form and an Anatomical Gift Act. The study was approved by the Institutional Review Board of Rush University Medical Center.

The study primarily recruits persons living communally, including employed (e.g., Teaching Orders) and retired (e.g., Missionary Orders) persons. The study includes three predominantly African American communities in New York, Baltimore, and New Orleans, and enrolls Hispanic sisters primarily from communities in and around San Antonio. All data collection forms have been translated into Spanish. Working with religious communities offers a number of advantages. First, they are altruistic and have a history of participating in research projects from which they may derive little to no personal benefit. Second, they live communally and loss of contact with participants is rare, facilitating the high follow-up and autopsy rates required to ensure internal study validity. Third, their wishes for organ donation are likely to be honored by the Superior and biological family members are unlikely to interfere with the participants' written preference. Finally, the participants have similar education, socioeconomic and life experiences for most of their adult lives. This allows for tighter control of these potentially confounding variables in analyses of incident AD and cognitive decline.

The study design (Figure 2) supports the following analyses in a single dataset: 1) the association of neurobiologic indices with AD, MCI, and cognition proximate to death and over multiple years prior to death; 2) the association of risk factors for incident AD, incident MCI, and cognitive decline; and 3) the modeling of neurobiologic pathways linking risk factors to clinical phenotypes. The collection of parkinsonian signs and other measures of motor function allow for similar analyses to be conducted with motor function and decline, and disability.

Demographic Variables and Socioeconomic Status

Race and ethnicity are ascertained using the 1990 U. S. Census questions. Measures of socioeconomic status include education and occupation. Birth address was linked to 1920 census data to determine early-life socioeconomic status [26]. Other indicators of early life socioeconomic status include parental education and occupation.

Clinical Diagnoses of Dementia, AD, MCI and Other Medical Conditions

Medical conditions are documented by clinical evaluation or self-report. To reduce costs and enhance uniformity of diagnostic decisions over time and space, a decision tree designed to mimic expert clinical judgment was implemented by computer to inform several clinical diagnoses, including dementia and AD [27,28]. It combines data reduction techniques for the cognitive performance testing with a series of discrete clinical judgments made in series by a neuropsychologist and a clinician, to develop presumptive diagnoses of dementia and AD. An algorithm uses these decisions to provide diagnoses of MCI and amnesic MCI [29,30]. Persons without dementia or MCI are categorized as no cognitive impairment (NCI)

[31]. The clinician is afforded an opportunity to override the decision tree diagnoses. The diagnoses of dementia and AD conform to the standard approach [7].

A similar decision tree approach also is employed to aid five other diagnoses including stroke, cognitive impairment due to stroke (vascular dementia), parkinsonism, Parkinson's disease (PD), and depression as described [32–37]. Other less common causes of dementia in community-based studies (e.g., Lewy body disease) are made by contemporary standards [38].

Most of the remaining diagnoses are by self report, including cardiovascular risk factors (e.g., hypertension, diabetes) and conditions (e.g., myocardial infarction, congestive heart failure, claudication) [39,40]. Tobacco and alcohol use is documented. Musculoskeletal pain is recorded [41]. Systolic and diastolic blood pressure is measured directly [40]. All over the counter and prescription medications are recorded. In some cases, clinical diagnoses used in analyses are supported by medication use [39,40]. Thus, a diagnosis of diabetes was based on self report and medication use (e.g., insulin). Sensitivity analyses are performed to ensure findings are not driven by inconsistent information (e.g., diabetes limited to persons on medications). We are also collecting hemoglobin A1c on a subset of participants.

Cognitive Performance Tests

A battery of 21 cognitive performance tests is administered each year (Table 1) [9,42–55]. The Mini-Mental State Examination (MMSE) [40] is primarily used to describe the cohort. Eleven tests are used for diagnostic classification [29]. Nineteen tests assess a range of cognitive abilities and are used to construct a global composite measure of cognition and separate summary measures of five cognitive domains, including episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. The composite measures are created by converting each test within each domain to a z-score and averaging the z-scores, as previously described [56]. Seven tests can be administered by telephone [57]. This version yields composites for episodic memory, semantic memory, and working memory, in addition to global cognition.

Motor Function and Structure

A detailed assessment of motor function is administered each year. The battery includes a modified version of the motor portion of the Unified Parkinson's Disease Rating Scale (mUPDRS) which is used to assess four parkinsonian sign domains including bradykinesia, rigidity, parkinsonian gait, and tremor, in addition to a composite global measure of parkinsonism [58–60]. This is supplemented by upper (e.g., finger tapping, Purdue pegboard, grip strength) and lower (e.g., walking speed) extremity motor performance tests [40,61–64]. Body mass index (BMI) is calculated from measured height and weight and is used as a measure of muscle structure [65].

Self Report Activities of Daily Living

Self-report measures assess the ability to live independently and perform basic and instrumental activities of daily living, and mobility disability [66–69]. Gait speed of 0.4 m/s is also used as a measure of performance-based mobility disability [41].

Risk Factors of Interest

Experiential factors include current cognitive and physical activities [70]. Affect includes measures of depressive symptoms, and state measures of anxiety and anger [71,72]. Personality includes measures of neuroticism, extroversion, openness, agreeableness, and conscientiousness, and trait measures of anxiety and anger [73,74].

Ante-Mortem Biological Specimens

Currently, a blood sample is taken at baseline and aliquots of serum and plasma are stored in a -80°C freezer. Lymphocytes are extracted to provide a source of DNA for genetic studies. Serum and DNA is available from nearly all participants at baseline. Plasma, for which collection started substantially later, is only available from about half of the cohort. About 350 persons have serum and plasma collected annually, and a urine for several years.

Ante-Mortem Biological Specimen Data

DNA has been used to characterize apolipoprotein E allele status (*APOE*) [75], and more recently, it has been used generate genome-wide genotyping data generated on a Affymetrix 6.0 platform and imputed to 2.2 million single nucleotide polymorphisms (SNPs) with HapMAP [76]. We are in the process of imputing additional SNPs with the 1000 genomes project. We are also in the process of generating Methylome-wide data with an Illumina 450 Beadchip.

Serum, plasma and urine are being used in a variety of add-on projects [77–79]. We are currently in the process of collecting anti-phospholipid antibodies and related indices for studies of cerebrovascular disease.

Post-Mortem Biological Specimens

Participants reside in more than a dozen states across the United States (Figure 1). Staff is on-call 24 hours per day, seven days a week, to coordinate transportation of the body, communicate with prearranged groups who help in performing autopsies outside of Chicago, and to perform autopsies at the Rush Alzheimer's Disease Center for local sites. The basic protocol is the same regardless of where the participant expires. The calvarium is opened, cerebrospinal fluid is removed, and the brain is removed and weighed. The brainstem and cerebellum are dissected from the hemispheres and one hemisphere and the cerebellum are cut into 1 cm slabs in a plexiglass jig. The 1 cm slabs are frozen in a -80°C freezer and the remainder of the brain is placed in 4% paraformaldehyde. Digital pictures of the hemispheres and slabs are obtained at the time of autopsy in Chicago and when the fixed hemisphere and frozen slabs are received from the outside autopsy groups. After paraformaldehyde fixation, the fixed hemisphere is cut into 1 cm slabs, photographed and tissue blocks are dissected from specified brain regions (including hippocampus, entorhinal cortex, anterior cingulate cortex, midfrontal cortex, superior frontal cortex, inferior temporal cortex, middle temporal cortex, inferior parietal cortex, primary occipital cortex, anterior basal ganglia, anterior thalamus, and midbrain) and paraffin embedded for subsequent histochemistry and immunocytochemistry. Gross features and pathology (e.g., atrophy, cerebrovascular disease) are described at the time of blocking, and blocks are obtained from all areas of visible pathology (e.g., infarctions, tumors) from direct observation or from the digital photographs. The remainder of the brain is transferred to a graded cryoprotectant solution (final solution of 20% glycerol and 2% DMSO in phosphate buffer) for long term storage at 4°C .

The protocol in Chicago is slightly more detailed as it also entails removal of spinal cord, muscle, and nerve on a subset, and post-mortem imaging on a subset.

Post-Mortem Data

The post-mortem neuropathologic evaluation includes a uniform structured assessment of AD pathology, cerebral infarcts, Lewy body disease, and other pathologies common in aging and dementia. The procedures follow those outlined by the pathologic dataset recommended by the National Alzheimer's Disease Coordinating Center (NACC) [80]. Pathologic diagnoses of AD use NIA-Reagan and modified CERAD criteria, and the staging of

neurofibrillary pathology uses Braak Staging [81–83]. The location, size, and age of each macroscopic infarct are recorded as described [35]. Microscopic infarctions are identified on H&E stained sections as is nigral degeneration; amyloid angiopathy is identified with amyloid immunostained sections; nigral, limbic, and neocortical Lewy bodies are identified on sections stained with α -synuclein [84–89].

Other post-mortem data are collected as part of separately funded projects. For example, counts of neuritic plaques diffuse plaques, and neurofibrillary tangles based on silver stain from five brain regions are used to create a global measure of AD pathology [75]. Amyloid load and the density of paired helical filament tau (PHFtau) are determined in eight brain regions and summarized [86]. More recently we have started to quantify TDP-43 [90].

Statistical Approaches

The study design allows for many different types of analyses that address a variety of issues related to the causes and consequences of common age related neurologic conditions, while controlling for potential confounding variables such as age, sex, and education, and others.

Cross-sectional analyses examining the relation of neuropathology to cognitive status proximate to death typically employ logistic regression for dichotomous outcomes (e.g., AD vs. no AD) and analysis of variance when examining difference across three diagnostic groups (e.g., NCI, MCI, and AD) with pairwise comparisons performed with the Tukey test [31]. Linear regression is used for continuous outcomes (e.g., level of cognition) [86]. We have also conducted a number of qualitative [75,86] and quantitative [91,92] mediation analyses which model a putative sequence of events using the cross sectional associations.

Longitudinal analyses examining the relation of risk factors to cognitive status typically employ Cox proportional hazards models for dichotomous outcomes (e.g., incident AD) [29,93]. More recently, we have used models for discrete (tied) data [94]. Other approaches such as accelerated failure models have been used when the assumptions of proportional hazards are not met [30]. Mixed models are used to examine the relation of risk factors to change in cognitive function over time [29,95]. In this approach individuals are assumed to follow the mean path of the group, conditional on a set of explanatory variables, except for random effects which cause the initial level of cognition to be higher or lower and the rate of change to be faster or slower. In situations for which the outcome has significant floor or ceiling effects that cannot be eliminated by data transformation, other approaches such as generalized estimating equations (GEE) have been used [96]. Change point models have also been used to characterize other paths of cognitive decline [97].

FINDINGS

From January of 1994 through October of 2011, 1,168 persons agreed to participate and the baseline clinical evaluation has been completed on 1,162. Of these, 806 (69.4%) are women, 1,023 (88.0%) are non-Hispanic white. Of 56 Hispanics, 8 are being tested in Spanish. The mean age is 75.7 years and the mean education is 18.1 years. 1,079 (92.9%) were without dementia following the baseline clinical evaluation.

The overall follow-up of survivors approaches 95%, and only 47 persons have withdrawn from the study since the first participants were evaluated in 1994. There have been 387 cases of incident MCI including 132 cases of incident amnesic MCI, and 287 cases of incident dementia including 273 cases of incident AD (with or without a coexisting condition), to date.

The autopsy rate approaches 95% with 539 autopsies of 574 deaths (93.9%). Of these, 343 (63.6%) are women, 511 (94.8%) are non-Hispanic white, the average age at death is 86.6 and the interval from last clinical evaluation to death is 9.0 months. The post-mortem interval is 8 hours 38 minutes. The MMSE proximate to death is 20.8 and the clinical diagnosis proximate to death includes 166 (31.0%) without cognitive impairment, 123 (23.0%) with MCI, 194 (36.3%) with probable AD, 38 (7.1%) with possible AD, and 14 (2.6%) with dementia due to another condition (four cases are currently under review). The diagnostic neuropathologic evaluation of the brain has been completed for the first 526 (97.6%).

Spinal cord, muscle and nerve have been obtained from 68 participants. Post-mortem brain imaging has been performed on 72 participants.

Relation of Common Neuropathologic Indices to Clinical AD, MCI, and Level of Cognition

Alzheimer's Disease Pathology—About 90% of persons meeting clinical criteria for AD also met pathologic criteria for the disease [27]. However, about half of persons with MCI also met pathologic criteria for AD [31,98]. Further, about a third of those without cognitive impairment met pathologic criteria for AD; however, among this group of very high functioning individuals, the presence of AD pathology was associated with deficits in episodic memory [99].

Mesial temporal lobe amyloid and neurofibrillary pathology were related to episodic memory across the spectrum of diagnoses [100–103]. Similar findings were found when amyloid and tau were assessed biochemically [104]. Using immunohistochemistry, amyloid load and PHFtau tangles were correlated. In multivariate regression models, tangles mediated the association of amyloid with cognition [86]. These data are consistent with a sequence of pathologic events in AD which begins with amyloid deposition and subsequent tangle formation.

Cerebrovascular Disease—Persons with dementia were more likely to have cerebral infarcts, and those with MCI had intermediate number of infarcts, compared to those without cognitive impairment [31,35,98,105]. Interestingly, while infarcts were related to all cognitive abilities, in analyses controlling for AD pathology, they were most strongly related to perceptual speed [35]. Further, AD pathology and cerebral infarcts had an additive effect on the odds of dementia [105]. Microscopic infarctions were also related to odds of dementia even after controlling for macroscopic infarcts and AD pathology [88]. Finally, cerebral amyloid angiopathy was also related to level of cognition, even controlling for measures of AD pathology and cerebral infarcts [89].

Lewy Bodies—Lewy bodies were most common in persons with dementia and intermediate among those with MCI [31,98]. Persons with MCI and dementia were more likely to have neocortical Lewy bodies even after controlling for AD pathology and infarcts [98]. When assessed biochemically, alpha-synuclein, the principal component of Lewy bodies, was also related to cognition [106].

Mixed Pathologies—The combination of AD pathology with cerebral infarcts or Lewy bodies is so common that mixed pathologies are the most common cause of dementia. Interestingly, mixed pathology is also as common as “pure” AD pathology as a cause of probable AD. In addition mixed pathology accounts for a substantial proportion of cases of both amnesic and non-amnesic MCI [98]. Consistent with this, all three pathologies are strongly related to multiple cognitive abilities, including episodic memory [107].

Relation of Neuropathology to Cognitive Decline—The design of the Religious Orders Study allows us to examine the relation of neuropathology not only to level of cognition proximate to death, but also to change in cognition over multiple years prior to death. In one study, we examined the relation of neuropathology to change basic lexical knowledge (i.e., word reading and vocabulary) over time, a skill which is thought to be relatively preserved in mild dementia and is often used to estimate premorbid ability. We found that the level of AD pathology, macroscopic cerebral infarctions, and neocortical Lewy bodies were all associated with rate of decline of lexical knowledge [108]. In fact, all cognitive abilities seem to dedifferentiate as cognition declines [109].

We used change point models to examine the influence of death on the trajectory of cognitive change prior to death, a concept called terminal decline [97]. We found that for those who die, the rate of cognitive decline accelerates more than six fold about four years prior to death. Next we incorporated neuropathologic indices into these models to explore their association with terminal and presumably disease related decline and the slower preterminal decline that could represent “normal” aging [110]. Neurofibrillary tangles and neocortical Lewy bodies contributed to disease-related cognitive decline, but substantial disease-related decline was evident even in the absence of these lesions. Neurofibrillary tangles, neocortical Lewy bodies, and cerebral infarctions all contributed to age-related cognitive decline. In fact little age-related decline was evident in the absence of these lesions suggesting that much of age-related cognitive decline is the result of these three common neuropathologies.

Another approach was also used to examine the relation of neuropathology to cognitive decline [111]. Profile mixtures models identified three classes of decliners, a slow class (65%), a moderate class (27%), and a rapid class (8%). Amount of AD pathology, especially tangles, was strongly related to class membership, with more AD pathology being associated with the rapid class of decliners.

Relation of Risk Factors to Incident AD and MCI, and Cognitive Decline (Table 2)

Age, Sex, and Education—Older age was associated with a more rapid rate of decline in all cognitive abilities [56]. Sex was not related to incident AD or to rate of cognitive decline [112]. Finally, education was not related to incident AD or rate of cognitive decline [70]. We also examined the influence of age, sex, and education on retest-effects, as this may have obscured associations with cognitive decline [113]. Adult cognitive activities also appeared to be of greater importance than years of education [114]. Although retest effects were substantial, they were not related to any of the demographic variables. Our index of early life socioeconomic status was related to level of cognition at baseline, but not to incident AD or cognitive decline [26].

Cognitive and Physical Activities—Participation in cognitively stimulating activities was associated with a reduced risk of AD and with a slower rate of cognitive decline [70]. The effect was rather selective for working memory and perceptual speed, two measures of processing resources. We also examined the relation of physical activity to risk of AD; although the point estimates were protective, the results were not significant [70].

Depressive Symptoms—Depressive symptoms were associated with an increased risk of AD and a more rapid rate of cognitive decline [36]. The effect was robust and cut across the full spectrum of cognitive domains. Because depressive symptoms may be an early sign of AD, we examined change in depressive symptoms during the prodromal phase of AD [115]. We did not find evidence of increasing depressive symptoms in the years immediately prior

to the development of AD suggesting that depressive symptoms are unlikely to be a consequence of declining cognition in preclinical AD.

Neuroticism and Conscientiousness—Neuroticism was associated with an increased risk of AD and with a more rapid rate of cognitive decline among persons without dementia, and risk of MCI and change in cognition among persons without dementia or MCI [116,117]. Interestingly, the association was most robust for episodic memory. By contrast, conscientiousness was associated with a reduced risk of AD and MCI, and a slower rate of cognitive decline [118]. The effect was robust and cut across the full spectrum of cognitive domains.

Measures of Motor Function and Structure—Progression of parkinsonian signs was associated with a greater risk of AD [119]. The effect was most robust for gait and rigidity. However, each parkinsonian sign was associated with decline in all five cognitive domains. Stronger grip strength was also associated with a reduced risk of AD [63]. Body mass index (BMI) was used as a measure of muscle structure. Loss of BMI was associated with an increased risk of AD and a greater rate of cognitive decline [65]. The findings were similar in analyses that examined weight loss.

Medical Conditions and Medications—A preliminary study found that cerebrospinal fluid levels of vitamin E were related to measures of AD pathology [120]. Diabetes was associated with an increased risk of AD and a more rapid rate of cognitive decline [39]. The association was relatively selective for perceptual speed, the domain most strongly related to cerebral infarctions [35]. Neither measured systolic or diastolic blood pressure was related to risk of AD or cognitive decline [121]. Neither use of non-steroidal anti-inflammatories nor aspirin was associated with risk of AD or cognitive decline [122]. Statin use was not associated with risk of AD or cognitive decline [123].

Apolipoprotein E Allele Status (APOE) and Other Genetic Variants—The *APOE* $\epsilon 4$ allele was associated with a greater risk of AD and rate of cognitive decline among persons without dementia, and greater risk of MCI rate of cognitive decline among those without dementia or MCI [94,124]. It was also associated with risk of AD among persons with MCI [125]. By contrast, the $\epsilon 2$ allele was associated with a slower rate of cognitive decline among those without dementia [126]. Interestingly, the associations for both alleles were most robust for episodic memory. *CR1* and *PICALM* were also associated with cognitive decline and AD risk [76]. An initial study case-control with cholesterol ester transfer protein (*CETP*) polymorphisms was null [127]. However, a follow-up found that the 1405V polymorphism was associated with cognitive decline, risk of AD, and with AD pathology [128].

We examined the association of other single nucleotide polymorphisms (SNP) with AD, including SNPs in the genes for brain-derived neurotrophic factor, and hepatic lipase which were null [129,130]. By contrast, the 211 haplotype of the low density lipoprotein receptor gene was associated with AD [131]. We also reported that a SNP which appears to modulate the splicing efficiency of low-density lipoprotein receptor was associated with increased AD odds in males [132].

Genome-wide data is now contributing to a number of studies of cognitive decline, meta-analyses, and candidate SNP analyses [133–141].

Relation of Risk Factors to Neuropathologic Indices (Table 3)

Association of Risk Factors with AD Pathology and Cerebral Infarctions—The *APOE* $\epsilon 4$ allele was associated with greater AD pathology and the $\epsilon 2$ allele was associated with less AD pathology [75,142,143]. AD pathology also mediated the association of the $\epsilon 4$ allele with clinical AD and level of cognition [15]. In other words, the cross sectional association between the $\epsilon 4$ allele and cognition was markedly reduced and no longer significant after accounting for AD pathology. Further, amyloid load mediated the association of the $\epsilon 4$ allele with level of cognition proximate to death, and to the presence of neurofibrillary tangles [143]. These data are consistent with a sequence of pathologic events in which *APOE* triggers a cascade of events eventually resulting in amyloid deposition and subsequent tangle formation. Similar findings were seen with *CR1* suggesting that this polymorphism was also associated with AD in part through an association with AD pathology [76]. The *PICALM* SNP reported in the GWAS AD case-control studies was not associated with AD pathology [76]. However, a separate SNP identified in a yeast model of AD did associate with measures of AD pathology [141]. Both the $\epsilon 4$ allele and *CR1* were also associated with amyloid angiopathy [144,145]. A number of other polymorphisms were related to AD pathology in a candidate gene study [146].

The *APOE* $\epsilon 4$ allele was also associated with macroscopic cerebral infarcts [144]. Further, in a series of mediation analyses, cerebral infarcts mediated the association of the $\epsilon 4$ allele with level of perceptual speed proximate to death [91,92]. Diabetes also was associated with macroscopic cerebral infarcts but not to measures of AD pathology [147].

Risk Factors that Modify the Relation of Neuropathology to Cognitive Function

—These analyses formally examine whether the relation between a risk factor and cognition differs by the amount of pathology. For example, while years of formal education were not directly related to measures of AD pathology, education modified the association of AD pathology with cognition [148]. In other words, a unit of AD pathology had much less effect on cognition among persons with more years of education. In further analyses, the effect was more strongly associated with amyloid deposition than with tangle formation [149].

We found AD pathology was more strongly related to clinical AD and level of cognition among women compared to men [150]. There was also a small direct effect such that women had more tangles.

While conscientiousness was also associated with a reduced risk of AD and a slower rate of cognitive decline, it was not associated with measures of AD pathology or cerebral infarctions. However, both neuropathologic indices modified the relation of conscientiousness to cognition [118]. Unexpectedly, the effect was in the opposite direction to what was predicted. In this case, both AD pathology and cerebral infarcts had a stronger association (i.e., reduced cognition further) among persons with more conscientiousness.

Risk Factors Associated with AD and Cognition Independent of Neuropathologic Indices

—Finally, a number of risk factors were neither directly related to measures of neuropathology nor did they modify the relation of neuropathology to cognition. These included depressive symptoms and neuroticism [116,151–153]. Interestingly, measures of psychological distress, based on a composite measure of depressive symptoms and the anxiety trait scale, were related to indices of dendrites and dendritic spines in the CA3 subfield of the hippocampus [154], a characteristic finding in animal models of chronic stress, and an area implicated in depression [155].

Selected Other Study Findings

Additional Studies of Mild Cognitive Impairment (MCI)—MCI was associated with an increased risk of developing AD and a greater rate of cognitive decline, especially episodic memory [29,30]. Persons with MCI had entorhinal cortex and hippocampal atrophy and disruption of parahippocampal white matter fibers [156]. They also had reductions of fractional anisotropy in posterior white matter regions [157]. Evidence of white matter changes were also found biochemically [158]. Finally, among persons with MCI, both baseline entorhinal cortex hippocampal volume and rate of change in entorhinal cortex and hippocampal volume are associated with risk of AD [159,160].

Relative to persons without cognitive impairment, persons with MCI have neuronal loss in layer II of the entorhinal cortex [161]. A number of studies examined the cholinergic system. Persons with MCI also had reduced neuron numbers in the cholinergic basal forebrain [162,163]. At the same time, there was an apparent upregulation of choline acetyltransferase activity in the hippocampus and frontal cortex, but not the primary visual cortex [164–1666]. While levels of nerve growth factors were maintained, it was not correlated with choline acetyltransferase activity [167]. Other neurotransmitter systems were investigated. The glutaminergic system was related to amyloid deposition and also appeared to be upregulated in MCI [168,169]. Changes in the GABAergic system were also described [170].

Relation of Factors to Motor Function, Disability, and Risk of Death—Diabetes was related to a more rapid change in parkinsonian signs, especially parkinsonian gait [171]. Change in parkinsonian signs, especially gait and rigidity was associated with an increased risk of death [37]. Systolic blood pressure was associated with a more rapid decline in lower extremity function assessed with quantitative measures of gait and balance [40]. While the effect persisted after controlling for vascular disease at baseline, it was attenuated when controlling for incident stroke suggesting that the effect might be mediated by cerebrovascular disease.

Parkinsonian signs, especially parkinsonian gait, were associated with a wide range of pathologies including nigral degeneration, nigral Lewy bodies, nigral neurofibrillary tangles, and cerebrovascular disease [87,172,173]. BMI was also associated with AD pathology and did not differ by dementia status [174].

Musculoskeletal pain was also associated with an elevated risk of mobility disability [41]. A greater number of joints affected was associated with a higher risk.

The personality traits of extraversion and conscientiousness were associated with a reduced risk of incident disability [175]. Psychological distress, depression, and suppressed anger were all associated with an increased risk of death whereas conscientiousness was associated with a reduced risk of death [176,177].

Studies of Implicit Memory—One class of implicit memory, repetition priming, is characterized by facilitation in speed or accuracy of processing an item as a result of prior exposure [178]. In contrast to episodic memory which show steady declines with age, measures of priming appear relatively stable over time, a finding that is not due to measurement instability [178,179]. Priming tasks known to draw on both visual-perceptual and conceptual processing were associated with slower rates of decline in activities of daily living, and visual-perceptual were associated with slower rates of progression of parkinsonian signs, especially parkinsonian gait [180,181]. Higher levels of neuropathology also related to lower levels of conceptual processing, or meaning-based but were not related to other priming tasks [182].

Other Neurobiologic Changes in Aging, MCI and AD—Mechanisms leading to cell death were also investigated including the role of nitric oxide-mediated neurodegeneration, and the role of caspase, Pin1, sirtuin 1, tissue transglutaminase, neprilysin, ryanodine receptor, and BDNF-TrkB signaling, in amyloid deposition, tangle formation, and neurodegeneration [183–195]. There also have been studies of oxidative stress, including astrocyte expression of heme oxygenase-1, oxysterol formation, and erythropoietin receptor expression [196–198]. Additional studies have examined inflammatory markers [199] and proteomics [200,201]. Tissue has been used to investigate the relation of amyloid deposits to amyloid imaging agents [202]. Genome-wide studies of aging and disability are also underway [203].

DISCUSSION

The Religious Orders Study has generated nearly 200 peer-reviewed publications to date on a wide range of issues related to aging and AD. The main findings can be summarized into four major headings: 1) continuum of cognition and neuropathology; 2) implications of mixed pathologies; 3) evidence of neural reserve; and 4) non-cognitive consequences of AD pathology.

Continuum of Cognition and Neuropathology from Normality to MCI to Dementia

Embedded within the US health care system is a categorical approach to disease. Patients, families, payers, and public health planners generally approach disease as something that is present or absent. However, many common chronic conditions of aging do not develop over minutes or hours or days such as a stroke or myocardial infarction. Rather, diseases such as osteoporosis and chronic obstructive pulmonary disease have an insidious onset that develops over years and possibly decades and the demarcation between the presence and absence of the disease is a matter of consensus criteria based on imperfect data. For some conditions, a designation intermediate between normality and disease is employed such as pre-hypertension and osteopenia. The situation is analogous for AD and MCI. Our data are most consistent with a continuum of cognitive change accompanied by a continuum of neuropathology with no precise clinical or neuropathologic cutpoint that distinguishes dementia from MCI or MCI from normality. In fact, using change point models, we recently found that about five to six years prior to the time a clinical diagnosis of AD is made, rate of cognitive decline sharply accelerates by about 15 fold [204]. In addition, MCI is also preceded by an accelerated rate of cognitive decline that begins nearly five years prior to diagnosis. Our findings are consistent with other studies that have addressed this issue [205–209]. These data suggest that much of cognitive decline among persons without dementia is not the result of a normative aging process but rather the result of the common neuropathologies that ultimately result in MCI and dementia. Further, these findings also suggest that there is unlikely to be qualitatively meaningful biologic distinctions between MCI and AD, regardless of the definition used. Our findings on AD contributed to the recent reconceptualization of AD as a condition that begins with an asymptomatic pathophysiologic process that progresses into MCI due to AD, followed by end stage dementia due to AD [210–212].

Implications of Mixed Pathologies for the Prevention of AD

Many groups have found that mixed pathologies contribute to dementia [213–218]. A major goal of the Religious Orders Study is to understanding biologic pathways linking risk factors to clinical disease. It turns out that among the risk factors investigated to date, only *APOE*, *CR1* and *CEPT* are strongly related to clinical AD through the AD pathology. And both *APOE* and *CR1* have other effects such as associations with cerebral infarctions and amyloid angiopathy. By contrast, because cerebral infarcts increase the odds of clinical AD,

risk factors for cerebral infarctions will also be risk factors for clinically diagnosed AD despite the absence of an association with AD pathology. Thus, we found that diabetes was likely related to clinical AD through an association with infarctions. However, the association is complex and other studies have reported a number of different findings [219–222]. These findings suggest that translating findings from epidemiologic studies to animal models should be done with caution [223]. Many animal models, such as transgenic models, are intended to investigate the role of amyloid deposition and tangle formation in the pathogenesis of AD. Further, the findings also suggest that association studies of pure AD will be biased since factors associated with co-morbidities will appear to be protective for AD. Our findings contributed to the development of new statement on the vascular contributions to cognitive impairment [224].

Evidence and Implications of Neural Reserve

Several experiential and psychological risk factors are related to clinical AD without evidence of having a direct effect on the accumulation of any of the three major neuropathologies linked to late life dementia. In some cases, the risk factor alters the relation of pathology to clinical outcomes. Others replicated our findings using both neuropathology and neuroimaging measures [225–228]. In other cases, such as depressive symptoms and psychological distress, the risk factor seems to have a separate but additive effect to the development of clinical disease. However, one study reported an association between depression and hippocampal AD pathology [229]. These findings suggest that there are unidentified neurobiologic pathways leading to cognitive decline. These could include neurodegeneration without a pathologic footprint. Alternatively, it may be that we are simply unable to identify the pathologic footprint based on current knowledge and abnormal proteins will be identified in the future. For example, in one preliminary study, variants in the *RELN* gene were associated with neuropathology among persons without dementia [140]. Together these data suggest that other neurobiologic indices must be important for the development of dementia [230]. Identifying these indices is important as they are potential new targets for therapeutic interventions. A variety of efforts are ongoing in the Religious Orders Study aimed at identifying additional therapeutic targets including epigenome-wide DNA methylation and histone acetylation studies, RNA expression studies, and proteomics.

Noncognitive Consequences of AD Pathology

We identified a number of motoric signs associated with risk of AD that are also related to AD pathology. Unlike *APOE* for which the temporal relation between the exposure and AD pathology is secure, and unlike diabetes for which there is ample evidence from other sources to suggest that it is a risk factor for cerebrovascular disease, it is difficult to imagine a scenario in which parkinsonian signs and BMI actually lead to the accumulation of AD pathology. Thus, a more parsimonious explanation is that these signs actually represent noncognitive clinical manifestations of AD pathology that are present prior to the time persons meet criteria for dementia. Our clinical findings have been observed in other cohort studies. Prior studies have reported a relation between parkinsonian signs and AD risk [231,232]. Further, prior clinical-pathologic studies have found a relation between nigral tangles and parkinsonian signs among persons with dementia [233–235]. However, we are unaware of prior studies that have examined these associations among persons without dementia. Clinical studies also show that low BMI and weight loss in old age is related to dementia risk [236–239]. We are not aware of other studies that have examined these associations with brain pathology.

Together, these data suggest that AD pathology is a cause of impaired motor function in older persons without dementia. For most neurologic diseases, the classic approach in neurology is to localize the lesions and then determine its etiology. Thus, for stroke and

brain tumors, for example, the clinical manifestation depends largely on the anatomic location. However, this approach is not currently employed for neurodegenerative diseases such as AD and Parkinson's disease (PD). These diseases are defined clinically and confirmed pathologically. There are many reasons related to the history of the field that has resulted in this development. However, it is much more likely that the location of AD pathology and Lewy bodies dictate the clinical expression of AD and PD and that loss of motor function can precede loss of cognition in AD, and likewise, loss of cognition can precede loss of motor function in PD.

Overall Model Summarizing Findings (Figure 3)

The model highlights the important role of mixed pathology in the development of AD, the finding that some risk factors work through as yet unidentified biologic pathways, and that AD and other pathology can lead to non-cognitive manifestations which may be evident prior to the development of overt dementia. Our finding that only genetic risk factors are associated with AD pathology have lead us to consider a model whereby AD pathology is primarily under the control of genetic variation. By contrast, experiential and psychological factors may primarily affect how your brain responds to the accumulation of pathology, i.e., neural or cognitive reserve.

Future studies are aimed at identifying additional risk factors and novel biologic pathways. For example, a genome wide association study is already underway seeking to identify additional genetic variants associated with AD pathology, in addition to variants associated with cognitive decline and incident AD [203]. In addition, two epigenome wide association studies currently are underway to examine other mechanisms that may link experiential and psychological phenotypes to cognitive decline. These include an epigenome-wide association study with DNA methylation using the Illumina 450 and an epigenome-wide association study of histone acetylation (H3K9Ac) using chromatin immunoprecipitation followed by sequencing (ChIP-Seq). Finally, post-mortem imaging is now being used to further investigate vascular disease [240,241].

Strengths and Weakness of the Study

The study has many strengths. Individuals are documented to be free of dementia or free of MCI at baseline and there is a large sample size and a relatively long duration of follow-up with repeated measures of cognition and large number of persons with incident AD and incident MCI. The follow-up rates of survivors and the autopsy rates are very high reducing the bias that occurs when select persons drop out of longitudinal studies or when autopsy is not obtained. Availability of postmortem specimens and data allow examination of underlying biologic mechanisms of disease. Structured procedures ensure uniformity of diagnostic decisions across time and space. Examiners are blinded to previously collected data further reducing bias. In addition, the similarity of lifestyle adds further control of potentially confounding variables.

The study also has limitations. The truncated range of socioeconomic status limits our ability to investigate these variables. For example, we did not find a relation of education to AD risk which could be due to truncated range of education; although we did find a relation of cognitive activity to AD risk [70]. Most cardiovascular risk factors are limited to self report. There are a restricted number of racial and ethnic minority clergy communities limiting their numbers in the study. It is an observational study and inferences regarding causality must be made with caution. Although, for many psychological and experiential risk factors, the effect sizes are likely to be small and cumulative and beyond the resolution of randomized clinical trials. Finally, it is a volunteer cohort of catholic clergy who must agree to autopsy at study entry and participants are not representative of any particular

population of older persons. Thus, similar types of studies will need to be done on cohorts with a much wider range of life experiences, in cohorts of racial and ethnic minorities, and in population based cohorts. In fact, the Religious Orders Study has data collection methods that are similar in many respects with other cohort studies, including the Memory and Aging Project and the Minority Aging Research Study, both the subject of a report in this volume. In addition, several risk factor associations have been replicated in the Chicago Health and Aging Project, a cohort study of incident AD in a geographically defined biracial population on the south side of Chicago [242]. These include late life cognitive activity, depressive symptoms, distress proneness, early life socioeconomic status, and use of anti-inflammatories [243–248].

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Figure 1.

Major locations of Religious Orders Study participants.*

* Archdiocesan Priests, Chicago, IL, Dubuque, IA and Milwaukee, WI; Benedictine monks, Lisle, IL, and Collegeville, MN; Benedictine Sisters, Erie, PA; Benedictine Sisters of the Sacred Heart, Lisle, IL; Capuchins, Appleton, WI; Christian Brothers, Chicago, IL, and Memphis, TN; Diocesan Priests, Gary, IN; Dominicans, River Forest, IL; Felician Sisters, Chicago, IL; Franciscan Handmaids of Mary, New York, NY; Franciscans, Chicago, IL; Holy Spirit Missionary Sisters, Techny IL; Maryknolls, Los Altos, CA, and Maryknolls, NY; Norbertines, De Pere, WI; Oblate Sisters of Providence, Baltimore, MD; Passionists, Chicago, IL; Presentation Sisters, BVM, Dubuque, IA; Racine Dominicans, Racine, WI; Salesian Sisters of St. John Bosco, San Antonio, TX; Sagrado Corazón, San Antonio, TX; Servites, Chicago, IL; Sinsinawa Dominican Sisters, Chicago, IL, and Sinsinawa, WI; Sisters of Charity, BVM, Chicago, IL, and Dubuque IA; Sisters of the Holy Family, New Orleans, LA; Sisters of the Holy Family of Nazareth, Des Plaines, IL; Sisters of Mercy of the Americans, Chicago, IL, Aurora, IL, and Erie, Pa; Sisters of St. Benedict, St. Cloud, MN and St. Joseph, MN; Sisters of St. Casimir Chicago, IL; Sisters of St. Francis of Mary Immaculate, Joliet, IL; Sisters of St. Joseph of La Grange, LaGrange Park, IL; St. Teresa De Jesus, San Antonio, TX.; Society of Divine Word, Techny, IL; Trappists, Gethsemane, KY and Peosta, IA; and Wheaton Franciscan Sisters, Wheaton, IL.

Figure 2.

Overall study design of the Religious Orders Study

Through October of 2011, the baseline evaluation has been completed on 1,162 persons.

There have been 387 cases of incident MCI and 287 cases of incident dementia (follow-up rate 95%), and 539 autopsies (autopsy rate 95%).

Figure 3.
Overview of clinical pathologic relationships reported in the Religious Orders Study through March 2010.

Table 1

Cognitive performance tests and their classification.

Test	Diagnosis	Composite	Telephone
Mini-Mental State Examination	Orientation		MMSE22
Logical Memory Ia		Episodic memory	
Logical Memory IIa		Episodic memory	
Immediate story recall		Episodic memory	Episodic memory
Delayed story recall	Memory	Episodic memory	Episodic memory
Word List Memory (3 trials)		Episodic memory	
Word List Recall	Memory	Episodic memory	
Word List Recognition	Memory	Episodic memory	
Complex Ideational Material	Language		
Boston Naming Test	Language	Semantic memory	
Category Fluency (fruits, animals)	Language	Semantic memory	Semantic memory
Extended Range Vocabulary		Semantic memory	
National Adult Reading test		Semantic memory	
Digit Span Forward		Working memory	Working memory
Digit Span Backward	Attention	Working memory	Working memory
Digit Ordering		Working memory	Working memory
Alpha Span		Working memory	
Symbol Digit	Attention	Perceptual speed	
Number Comparison		Perceptual speed	
Judgment of Line Orientation	Visuospatial	Visuospatial ability	
Standard Progressive Matrices	Visuospatial	Visuospatial ability	

Table 2

Factors related to incident AD and MCI, and cognitive decline.

Risk Factor	Incident AD	Cog Dec ^[1]	Incident MCI	Cog Dec ^[2]
Age	X	X		
Cognitive activity	X	X		
Depressive symptoms	X	X		
Neuroticism	X	X	X	X
Conscientiousness	X	X	X	
MCI	X	NA	NA	NA
Parkinsonian signs	X	X		
Grip strength	X			
Decline in BMI	X	X		
Diabetes	X	X		
<i>APOE</i> ε4	X	X	X	X
<i>APOE</i> ε2		X		
<i>CR1</i>	X	X		
<i>PICALM</i>		X		
<i>CEPT</i>	X	X		

^[1] cognitive decline among persons without dementia at baseline

^[2] cognitive decline among persons without dementia or MCI at baseline

Table 3

Relation of risk factors for AD to neuropathologic indices.

Risk Factor	Related to pathology	Modifies relation of pathology to cognition
<i>APOE</i> ϵ 4	AD, Infarcts	
<i>APOE</i> ϵ 2	AD	
<i>CR1</i>	AD	
<i>CEPT</i>	AD	
Parkinsonian signs	AD	
PICALM	Unrelated	No effect modification
BMI	AD	
Diabetes	Infarcts	
Education		AD
Sex	AD	AD
Conscientiousness		AD, Infarct
Depressive symptoms	Unrelated	No effect modification
Neuroticism	Unrelated	No effect modification