Title: Combined neuropathological pathways account for age-related risk of dementia

Running Head: Multiple pathologies and age-related dementia risk

Authors and Affiliations:
Melinda C. Power, ScD[1], Elizabeth Mormino, PhD[2], Anja Soldan, PhD[3], Bryan D. James, PhD[4,5], Lei Yu, PhD[6], Nicole M. Armstrong, PhD[7], Katherine J. Bangen, PhD[8,9], Lisa Delano-Wood, PhD[8,9], Melissa Lamar, PhD[4,10], Yen Ying Lim, PhD[11], Kelly Nudelman, PhD[12], Laura Zahodne, PhD[13], Alden L. Gross, MHS, PhD[7,14,15], Dan Mungas, PhD[16], Keith F. Widaman, PhD[17], Julie Schneider, MD[4,6,18]

[1]Department of Epidemiology and Biostatistics, George Washington University Milken Institute School of Public Health, Washington, DC; [2]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; [3]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD; [4]Rush Alzheimer's Disease Center, Rush University, Chicago, IL; [5]Department of Internal Medicine, Rush University, Chicago, IL; [6]Department of Neurological Sciences, Rush University, Chicago, IL; [7]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [8]VA San Diego Healthcare System, San Diego, CA; [9]Department of Psychiatry, University of California San Diego, San Diego, CA; [10] Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL; [11]Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia; [12]Department of Radiology and Imaging Sciences, Indiana University-Purdue University at Indianapolis, Indianapolis, IN; [13]Department of Psychology, University of Michigan, Ann Arbor, MI; [14]Johns Hopkins Center on Aging and Health, Baltimore, MD; [15]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [16]Department of Neurology, University of California - Davis, Davis, CA; [17]Graduate School of Education, University of California Riverside, Riverside, CA; [18]Department of Pathology, Rush University Medical Center, Chicago, IL

Corresponding Author:
Melinda C. Power
George Washington University Milken Institute School of Public Health
950 New Hampshire Avenue NW, Washington DC 20052
Power@gwu.edu
T: 202.994.7778 ; F: 202.994.0082

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ABSTRACT

Objective: Our objectives were to characterize the interrelation of known dementia-related neuropathologies in one comprehensive model and to quantify the extent to which accumulation of neuropathologies accounts for the association between age and dementia.

Methods: We used data from 1,362 autopsied participants of three community-based clinico-pathologic cohorts: the Religious Orders Study, the Rush Memory and Aging Project, and the Minority Aging Research Study. We estimated a series of structural equation models summarizing *a priori* hypothesized neuropathological pathways between age and dementia risk individually and collectively.

Results: At the time of death (mean age: 89 years), 44% of our sample had a clinical dementia diagnosis. When considered individually, our vascular, amyloid/tau, neocortical Lewy body, and TAR DNA-binding protein 43 (TDP-43)/hippocampal sclerosis pathology pathways each accounted for a substantial proportion of the association between age and dementia. When considered collectively, the four pathways fully accounted for all variance in dementia risk previously attributable to age. Pathways involving amyloid/tau, neocortical Lewy bodies, and TDP-43/hippocampal sclerosis were interdependent, attributable to the importance of amyloid beta plaques in all three. The importance of the pathways varied, with the vascular pathway accounting for 32% of the association between age and dementia, while the remaining three interrelated degenerative pathways together accounted for 68% (amyloid/tau: 24%, the Lewy body: 1%, and TDP-43/hippocampal sclerosis: 43%).

Interpretation: Age-related increases in dementia risk can be attributed to accumulation of multiple pathologies, each of which contributes to dementia risk. Multi-pronged approaches may be necessary if we are to develop effective therapies.

INTRODUCTION

Multiple age-related neuropathologies are increasingly recognized as contributors to dementia risk.[1-6] Although dementia is most commonly associated with Alzheimer's disease (AD) neuropathology, namely amyloid beta plaques and neurofibrillary tangles, pure AD is relatively rare; the majority of dementia cases clinically diagnosed with probable AD show evidence of multiple neuropathologies.[4, 7-11] Even among pathologically confirmed AD cases, significant co-morbidities are common and are frequently associated with worse clinical outcomes. For instance, for a given level of AD neuropathology, the presence of infarcts[12] or cortical microinfarcts[13] is associated with greater cognitive impairment, suggesting that underlying vascular disease increases dementia risk independent of AD neuropathology. Cerebral amyloid angiopathy (CAA), which commonly co-exists with AD pathology and which is associated with other features of cerebrovascular disease,[14] is also independently associated with cognitive impairment and dementia.[15, 16] Although Lewy bodies can contribute to dementia risk in the absence of AD neuropathology, Lewy bodies are common in persons with pathologically confirmed AD,[17, 18] and individuals with both AD pathology and Lewy bodies show greater risk of cognitive decline or dementia.[19-21] Likewise, TAR DNA-binding protein 43 (TDP-43) aggregations are common in aging, in pathologically confirmed AD, and in combination with hippocampal sclerosis, [22, 23] and TDP-43 aggregations increase the likelihood of dementia, including a clinical diagnosis of AD.[7, 24]

The extent to which these neuropathological pathways interrelate and whether known neuropathologies can fully account for age-related increases in dementia risk is currently unknown. A fuller understanding will be critical to the development and targeting of effective therapies. Using structural equation modeling (SEM), we tested the significance and interrelations of all major dementia-related neuropathologies by which age was hypothesized to elevate dementia risk in an autopsy sample of persons recruited from the community.

METHODS

Study Sample

We used clinical and neuropathological data from autopsied participants of three Rush Alzheimer's Disease Center clinical-pathologic cohorts of aging: the Religious Orders Study (ROS),[25] the Rush Memory and Aging Project (MAP),[26] and the Minority Aging Research Study (MARS).[27] Briefly, ROS began in 1994 and recruited older Catholic nuns, priests, and brothers from religious orders across the United States. Participants were enrolled from over 40 groups and included communally-living employed and retired persons. MAP began in 1997 and recruited older adults living in retirement communities and subsidized housing facilities across the Chicago metropolitan area. MARS began in 2004 and recruited older adults who self-identified as African American or Black from churches, subsidized senior housing facilities, retirement communities, clubs, and organizations in the Chicago metropolitan area. Recruitment efforts involved relationship-building with local communities and consultation with community-based advisory groups. These three cohorts are designed to allow combined analyses. For all three, eligibility criteria required absence of recognized dementia at recruitment and agreement to annual clinical evaluations and cognitive testing. Participation in ROS and

MAP required brain donation at death. MARS participants were asked, but not required, to donate starting in 2010. At the time of writing, the three studies had enrolled 4,094 subjects, and follow-up rates exceeded 90% of survivors. All three studies were approved by the institutional review board of Rush University Medical Center. All participants in our sample signed an informed consent and an Anatomical Gift Act form.

At the time of analyses, 1,744 participants had died and autopsies had been completed on 1,418 (81.3%) participants. Our sample consists of the 1,362 persons with valid neuropathology data and a final consensus cognitive diagnosis of cognitive status prior to death.

Measures

Age at death was based on self-reported date of birth and known date of death. Cognitive diagnosis proximate to death was determined by a neurologist with expertise in dementia who reviewed the available clinical data (i.e. interview data, medical history and examination data, neuropsychological testing, and annual diagnostic classification). For difficult cases, diagnosis was ascertained by consensus at a case conference including at least one neurologist and one neuropsychologist. All cognitive diagnoses were made blinded to postmortem data. AD dementia was classified according to NINCDS-ADRDA criteria; [28] less common dementia subtypes were classified according to accepted criteria or contemporary standards.[29-31] For this analysis, Individuals with a dementia diagnosis according to any dementia criteria were classified as having dementia.

Brain autopsies were standardized and completed by study personnel blinded to clinical information.[4, 32, 33] Briefly, each brain hemisphere was cut in coronal 1-inch slabs. One hemisphere was fixed in 4% paraformaldehyde and then cut, while the other was immediately photographed and frozen.

Regions of interest were dissected from the fixed slabs and embedded in paraffin; sections of the paraffin blocks were cut and stained to characterize pathologies. All measures were reviewed by a board-certified neuropathologist.

Neuritic plaques and neurofibrillary tangles (tangles) were counted during microscopic examination of Bielschowsky silver-stained 6 micron sections on slides from 5 regions (hippocampus, midfrontal cortex, midtemporal cortex, inferior parietal cortex, and entorhinal cortex). Total number was counted within a 1 mm^2 area of apparent greatest density of each index. We scaled regional counts of neuritic plaques and tangles by dividing the count of each region by the corresponding standard deviation. Scaled regional counts of neuritic plaques were averaged to provide a single neuritic plaques summary measure. Latent variable summaries of mesiotemporal and neocortical tangles were derived from scaled regional counts of tangles for use in analyses. Fixed slabs or photographs were evaluated for evidence of gross infarcts; we quantified gross infarcts as counts of visualized, dissected, and histologically confirmed chronic macroscopic infarcts. Paraffin-embedded sections from a minimum of 9 brain regions stained with hematoxylin/eosin (midfrontal cortex, middle temporal cortex, inferior parietal cortex, entorhinal cortex, hippocampus cortex, basal ganglia, thalamus, and midbrain) were used to characterize burden of microinfarcts, defined as infarcts identified by microscopy but not gross visual examination. We considered the count of ascertained microinfarcts across all sections. Macroscopic and microscopic infarct counts were parameterized as 0, 1, or ≥2 infarcts. Neuropathologists characterized cerebral atherosclerosis, arteriolosclerosis, and CAA using an ordinal scale ranging from 0 (none) to 3 (severe). Ratings of atherosclerosis were based on visual examination of the Circle of Willis, arteriolosclerosis was quantified based on evaluation of the small vessels of the

anterior basal ganglia, and CAA was assessed based on evaluation of paraffin-embedded sections of four

neocortical regions (midfrontal, middle temporal, inferior parietal, and occipital) immunostained for

beta-amyloid (antibody, Covance Labs, Dako, or Elan Pharmaceuticals).[32] Lewy body disease was

ascertained as present, brainstem-predominant, limbic-type, or neocortical-type based on evaluation of

alpha-synuclein immunostained sections (antibody, Zymed or Wako) from multiple brain regions and a

modified version of the McKeith criteria.[34] We considered only the presence or absence of neocortical

Lewy body disease, as only neocortical Lewy bodies appear related to dementia.[35] Severity of TDP-43

was quantified across six brain regions (amygdala, hippocampus CA1, hippocampus dentate, entorhinal

cortex, middle temporal cortex, and midfrontal cortex) based on the number of cytoplasmic inclusions

observed in the 0.25 mm^2 area of greatest density after immunostaining for monoclonal antibodies to

phosphorylated TDP-43 (antibody, Ascenion). Each region was reviewed for neuronal and glial inclusions

and rated on an ordinal 6-point scale. Total TDP-43 severity was quantified as the mean rating across the

six regions. Hippocampal sclerosis was detected using H&E staining and the presence of severe neuronal

loss in CA1 hippocampal subfield and/or subiculum. See

http://www.radc.rush.edu/docs/var/variables/htm for additional details.

Statistical Methods

We used SEM to estimate models including both latent and manifest variables that summarized

our *a priori* hypothesized neuropathologic pathways between age and dementia risk, described below.

These analyses tested whether our hypothesized models were consistent with the data and estimated

the strength and significance of each hypothesized relation in our model. We estimated all parameters

using weighted least squares with standard errors and mean- and variance-adjusted test statistics with a

full weight matrix (WLSMV) which yields parameter estimates and standard errors that are robust to violations of multivariate normality. This method yielded measures of model fit and allowed use of data from all participants, even if data on certain variables were missing for some participants. Because several variables in our models were categorical, we report standardized parameter estimates from WLSMV estimation to enable more direct comparisons of magnitude of effects for different pathways to dementia. We used the χ^2 statistic and several practical fit indices when evaluating model fit to data, including the root mean square error of approximation (RSMEA), comparative fit index (CFI), Tucker-Lewis index (TLI), and standardized root mean square correlation (SRMR). An RSMEA ≤ 0.05, CFI > 0.95, TLI > 0.95, and SRMR < 0.08 indicate close model fit to data.[36]

To begin, we used confirmatory factor analysis (CFA) to model latent variables summarizing a subset of pathologies. *A priori*, we hypothesized a latent variable for (a) *vessel disease*, informed by measures of arteriolosclerosis and atherosclerosis, (b) *infarcts*, informed by measure of gross and micro cerebral infarcts, (c) *neocortical tangles*, informed by tangles in the inferior parietal, midfrontal, and midtemporal cortices, and (d) *mesiotemporal tangles*, informed by tangles in the entorhinal and hippocampus cortices. Assessment of model fit supported a modification allowing midtemporal tangles counts to inform both the neocortical and mesiotemporal tangles latent constructs. This alternate parameterization was added to our *a priori* hypothesized path model (summarized with this modification in Figure 1) and was used in all subsequent SEM models involving this pathology. Use of alternate scorings for the cerebral infarct indicators did not appreciably change CFA results. Results of the CFA are available in Table s1.

After building these measurement models, we considered a series of structural models. Model 0

characterized the overall relation of age and dementia. Models 1 to 4 characterize four *a priori* hypothesized pathologic pathways thought to mediate the association of age and dementia: a vascular pathway (Model 1), an amyloid/tau pathway (Model 2), a Lewy body disease pathway (Model 3), and a TDP-43/hippocampal sclerosis pathway (Model 4). Finally, we considered a full model (Model 5, Figure 1) incorporating all four pathways and their hypothesized interrelations.

We conducted several sensitivity analyses. First, to consider other paths considered but excluded from our *a priori* model, we evaluated whether there was statistical justification for adding a path from infarcts to neuritic plaques, a path from neuritic plaques to hippocampal sclerosis, or a path from CAA to infarcts. Second, we used two-group modelling to determine whether results varied across data source (MAP and ROS; MARS participants were excluded due to small numbers of MARS participants), across sex, or across persons from different birth cohorts. Two-group analyses of birth cohort addressed concerns that the distribution of pathologies could differ across those who died early or late relative to their peers. If so, then our sample would be enriched in pathologic patterns characteristic of those who died prematurely and our results would not be generalizable. Thus, we defined a group born before 1915, who would be extremely unlikely to remain alive through the end of our sampling period and compared whether our structural model was consistent in those born before 1915 (who are representative of all dead individuals) and those born after 1915 (enriched in those who died prematurely). For each of our two-group comparisons, we confirmed measurement invariance prior to proceeding. All statistical analyses were completed using Mplus (Version 8) or STATA (Version 14). Throughout, we consider a p-value <0.05 to be statistically significant.

RESULTS

The demographic and clinical characteristics of our sample are summarized in Table 1. On average, our sample was 89 years old at death (range: 65 to 108). Of the 44% with a clinical dementia diagnosis prior to death, 85% were diagnosed with AD dementia without a second cause of cognitive impairment, 11% were diagnosed with AD dementia with a second cause of cognitive impairment (e.g., stroke), and 4% were diagnosed with a non-AD primary cause of dementia. Brain pathology at autopsy was common regardless of dementia status. Age was significantly related to risk of dementia (OR: 1.79, 95% CI: 1.51, 2.12 per 10 years increase in age). This is represented by a standardized coefficient of 0.24 standard deviation (SD) units (SE = 0.03); see Table 2 (Model 0).

Model 1: Vascular Pathway

To model the vascular pathway, we allowed the relation between age and dementia to be mediated by latent variables for vessel disease and infarcts (Figure 2, Table 2: Model 1). Age had a significant direct effect on vessel disease, but not on infarcts. Vessel disease had a strong association with infarcts. Both vessel disease and infarcts had significant, independent associations with dementia. However, the direct effect of age on dementia remained large and significant (standardized coefficient β = 0.16, SE = 0.04).

Model 2: Amyloid/tau pathway

Next, we considered an amyloid/tau pathway, allowing the relation between age and dementia to be mediated by neuritic plaques, our neocortical and mesiotemporal tangles latent variables, and CAA (Table 2: Model 2). *A priori*, age was specified to have direct effects on neuritic plaques, neocortical

tangles, mesiotemporal tangles, and CAA, in addition to its direct effect on dementia. Neuritic plaques were hypothesized to have direct effects on neocortical tangles, mesiotemporal tangles, and CAA. In turn, the two tangles latent variables and CAA were hypothesized to have direct effects on dementia. In considering potential modifications, the addition of a direct effect of neuritic plaques on dementia (Table 2: Model 2a) improved model fit; we accepted the model with this modification as the final amyloid/tau model. Parameter estimates for Model 2a are shown in Figure 3. Age had significant direct effects on neuritic plaques, mesiotemporal tangles, and CAA, but not neocortical tangles. Neuritic plaques had significant direct effects on neocortial tangles, mesiotemporal tangles, CAA, and dementia. The neocortial tangles latent variable had a significant effect on dementia, as did CAA, but the effect of the mesiotemporal tangles factor on dementia was non-significant. As with the vascular model, when considered independently, the amyloid model only partially mediated the effect of age on dementia, as the direct effect of age on dementia remained substantial and significant (standardized coefficient β = 0.21, *SE* = 0.03).

Model 3: Lewy body pathway

Third, we considered a neocortical Lewy body pathway. We hypothesized that age would have direct effects on neuritic plaques, presence of neocortical Lewy body disease, and dementia; that neuritic plaques would have a direct effect on neocortical Lewy body disease; and the neocortical Lewy body measure would have a direct effect on dementia. This model had very poor fit (Table 2: Model 3). The only possible modification was to include a direct effect of neuritic plaques on dementia. The modified model (Table 2: Model 3a) was saturated, and was accepted as the final Lewy body model. However, this result suggested that considering the Lewy body pathway separately from the

amyloid/tau pathway or other hypothesized pathways involving neuritic plaques is inappropriate.

Parameter estimates for Model 3a are shown in Figure 4. Age had a small direct effect on neuritic

plaques and a non-significant, essentially zero direct effect on Lewy body pathology. Neuritic plaques

had significant effects on both Lewy body pathology and dementia. Lewy body disease had a substantial

direct effect on dementia. As in previous models, the direct effect of age on dementia (standardized

coefficient β = 0.21, *SE* = 0.03), remained large and significant, indicating that the neocortical Lewy body

disease pathway only partially mediated the age-dementia relation.

Model 4: TDP-43/hippocampal sclerosis pathway

Fourth, we considered a pathway involving TDP-43 and hippocampal sclerosis. Because neuritic

plaques were again implicated in TDP-43 and hippocampal sclerosis, these three variables were included

a priori along with age and dementia. The *a priori* form of Model 4 assumed that neuritic plaques would

affect dementia only indirectly through its effects on TDP-43 and hippocampal sclerosis, but had poor fit

to the data (Table 2: Model 4). This again necessitated the addition of a direct path from neuritic

plaques to dementia, resulting in Model 4a (Table 2: Model 4a), which had very good fit and was

accepted as the final model. However, as above, this indicated that considering TDP-43 and

hippocampal sclerosis independent of other pathways involving neuritic plaques may not be

appropriate. Parameter estimates for Model 4a are shown in Figure 5. Age had direct effects on both

TDP-43 and hippocampal sclerosis. Neuritic plaques had a significant effect on TDP-43. Both neuritic

plaques and hippocampal sclerosis had relatively large effects on dementia, but the direct effect of TDP-

43 on dementia was non-significant. However, the direct effect of age on dementia (standardized

coefficient β = 0.11, *SE* = 0.04) remained significant, indicating that the TDP-43/hippocampal sclerosis

pathway did not fully mediate the age-dementia relation.

Model 5: All pathologies combined

We then considered a model incorporating all four pathways simultaneously (Figure 1). This

model fit the data well (Table 2, Model 5). However, five path coefficients were non-significant: the

effects of age on infarcts, neocortical tangles, and Lewy body disease; the effect of vessels on neuritic

plaques; and the effect of TDP-43 on dementia. When these five path coefficients were fixed at zero, the

resulting model had slightly improved fit to the data (Table 2: Model 5a). However, as this has little

appreciable impact on the fit (Table 2), parameter estimates (Table s2), or percentage of the effect of

age on dementia mediated by each path, we discuss Model 5 here and in Figure 6.

Direct effects of variables on one another are similar to those discussed for the modeling of

separate pathways, although the addition of a direct path between neuritic plaques and dementia,

added to improve model fit in Models 2a, 3a, and 4a, was not necessary here. Model fit worsened

significantly if the path coefficients associated with any particular sub-model (e.g., the path coefficients

contained in the vascular pathway) were fixed to zero. Similar worsening of model fit occurred if

previously important individual path coefficients were fixed at zero. Unlike in the models for the

individual pathways, the direct effect of age on dementia in Model 5 was essentially zero, (standardized

coefficient: $\beta = 0.01$, *SE* = 0.04) and non-significant; thus, the four pathways to dementia, taken

together, fully mediated the relation between age and dementia. In this combined model, the vascular

pathway accounted for 32% of the association between age and dementia, while the remaining three

pathways, all of which involved neuritic plaques, accounted for 68% (the amyloid/tau pathway

accounted for 24%, the Lewy body pathway accounted for 1%, and the TDP-43/hippocampal sclerosis

pathway accounted for 43%). (Recognizing that CAA can also be considered a vascular pathology, if we add the paths through CAA to our previously defined vascular pathway, these collectively account for 36% of the association between age and dementia.)

Sensitivity analyses were consistent with primary analyses. There was no evidence to support the addition of paths from infarcts to neuritic plaques, neuritic plaques to hippocampal sclerosis paths, or CAA to infarcts (all p>0.3). No significant differences in Model 5 were found by sample source (MAP versus ROS) or by sex.[37, 38] When dividing our sample into those born before or after 1915 and allowing the path coefficients to be estimated freely, the statistical index of fit worsened notably ($\chi^2(176)$ = 276.97, $p < .001$), but the model had excellent global fit (RMSEA: 0.029, CFI: 0.987, TLI: 0.983). Further analyses suggested allowing the path coefficient from neuritic plaques to neocortical tangles to differ across groups; the resulting model had improved statistical model fit ($\chi^2(24)$ = 23.62, $p = .48$) and the standardized coefficient was $\beta = 0.41$ ($SE = 0.01$) for those born before 1915, and $\beta = 0.57$ ($SE = 0.01$) for those born after 1915, indicating a difference in magnitude but not presence or direction of association across groups.

DISCUSSION

Overall, our results demonstrate that accumulation of known pathologies, including cerebrovascular disease, amyloid/tau, CAA, neocortical Lewy bodies, TDP-43, and hippocampal sclerosis, completely account for the increased risk of dementia with age. In the combined model, all four pathways remain important, indicating that each pathway uniquely contributes to the age-related increase in risk of dementia. Our models also suggest interrelations between the amyloid/tau, Lewy body, and TDP-43/hippocampal sclerosis pathways. Specifically, neuritic plaques appear related to

neurofibrillary tangles, CAA, neocortical Lewy body disease, and TDP-43, and after accounting for the association between neuritic plaques and these other pathologies, neuritic plaques had no direct effect on dementia. This suggests a significant contribution of amyloid beta to dementia through multiple pathways, not simply through influence on tangles. Importantly, although neuritic plaques appeared related to CAA and TDP-43/hippocampal sclerosis, these pathologies also appear to mediate the elevated risk of dementia on age through pathways that do not involve neuritic plaques. Finally, our model supports independence between the collective influence of the amyloid/tau, Lewy body, and TDP-43/hippocampal sclerosis pathways from our vascular pathway, with the vascular pathway accounting for 32% of the variance in dementia risk attributable to age, and the remaining pathways collectively accounting for 68%.

This work is generally consistent with prior work. Multiple studies have shown that vascular, amyloid/tau, Lewy bodies, and TDP-43/hippocampal sclerosis pathologies all contribute to cognition in older ages.[8] Interestingly, despite suggestion of a synergistic relation in other contexts[12], our work confirms prior work in ROS/MAP and elsewhere suggesting that vascular pathology does not interact with AD pathology to promote dementia.[3, 39-41] Nonetheless, the relative contribution of various pathologic pathways may differ by cognitive outcome. For example, in prior work in ROS/MAP, a vascular pathway accounted for 20% of variance in the association between age at death and pre-death decline in episodic memory and 29% of the variance in the corresponding association with decline in non-episodic memory.[42]

Little is known about the impact of TDP-43 and hippocampal sclerosis on cognition and

dementia, alone or in the context of other pathologies. In the current analysis, the effect of TDP-43 on dementia risk was completely mediated by hippocampal sclerosis. However, we and others have reported that TDP-43 is independently associated with worse episodic memory, cognitive decline, and increased odds of dementia.[7, 43, 44] The source of this discrepancy remains unknown. Potential reasons include the omission of other pathologies in prior work, unique or synergistic effects of hippocampal sclerosis and TDP-43 on domain-specific cognition, or the sparsity of persons in our sample with hippocampal sclerosis but no TDP-43 (n=11). Because hippocampal sclerosis has been reported to be segmental,[45] neuropathological assessment of multiple sections of hippocampus may be necessary to fully characterize the condition. Regardless, further work on the relation among AD, TDP-43, and hippocampal sclerosis is warranted, particularly given that pathways involving these pathologies appear to mediate a large percentage of the age-related increase in dementia risk.

Our study extends prior attempts to characterize the collective impact of multiple pathologies on cognition in several important ways. Our study included all major pathologies thought to contribute to dementia risk, which, combined with an SEM approach, allowed us to describe and quantify the relative contributions of hypothesized pathways, not just individual predictors. Notably, use of SEM allowed us to think globally about complex causal relationships between pathologies, enabled by the use of latent variables, simultaneous consideration of individual variables as both predictors of an outcome and mediators of a different predictor-outcome relation, and established methods to assess overall motel fit. Our approach also addresses the novel question of whether the collective influence of known pathologies can account for the association between age and dementia risk. Prior studies have frequently considered only a subset of pathologies, taken a different approach, or addressed related,

but distinct questions. For example, in prior work in ROS/MAP, global Alzheimer pathology, amyloid, tangles, gross infarcts, microinfarcts, and neocortical Lewy bodies accounted for 41% of the total variance in the rate of cognitive decline prior to death.[32] While this study was limited by omission of TDP-43, hippocampal sclerosis, and measures of vessel disease, it appears unlikely that 100% of the variance would be accounted for after inclusion of these additional factors. However, the conclusion that pathology cannot fully account for variation in cognitive decline is not necessarily at odds with our findings here. While we conclude that accumulating pathology fully mediated the elevation in risk of dementia observed with age, we did not address the related question addressed in this prior study of whether differences in pathology account for variance in measures of cognition among similarly aged persons.

This study had many strengths. Our large clinico-pathologic sample was recruited from the community prior to the known onset of dementia, and autopsies were performed on the vast majority of deceased participants. In addition, our conclusions were consistent across data sources, birth cohorts, and sex. Our results are arguably generalizable to the white general population. The study also benefited from high-quality clinico-pathologic data quantifying all the major dementia-related pathologies and study-based clinical dementia ascertainment derived from in-person examinations, which is less prone to misclassification than ascertainment based on medical records or similar sources.

This study also has limitations. Some degree of misclassification is expected. However, despite expected misclassification, we were able to account for all the variance in clinical dementia status associated with increasing age. Our data were cross-sectional. Thus, we cannot prove the temporal

ordering or causal relations implied by our model. We can only conclude that our hypothesized model is

or is not consistent with the data; we cannot conclude that we have identified the true underlying causal

relations. Other hypothesized models may also fit the data and may or may not better reflect the true

underlying causal structure connecting age, neuropathology, and dementia. Our results may not be

generalizable to all race/ethnic groups. Whether there are differences in prevalence of brain pathologies

across race/ethnic groups remains unclear[46-48] and whether such differences would translate into

differences in the relative importance of particular pathways remains unknown. Similar work in more

diverse samples is warranted. The relative contribution of various pathologic pathways may differ by

cognitive outcome[42] or by presence of specific genetic polymorphisms.[49, 50] Future work should evaluate

this possibility. Finally, we considered broad characterizations of neuropathologic pathways. More

detailed models (e.g.,[51]) may reveal further insights. In particular, our models do not account for all

vascular pathologies (e.g., microbleeds, damaged neurovascular unit, etc.) or functional/molecular

processes (e.g., contractility, glymphatic drainage, etc.).

   Our findings have significant implications for clinical trial design and drug discovery. Efforts to

develop therapies for AD have long targeted amyloid. While our analyses support the supposition that

an effective anti-amyloid medication may have benefit on multiple pathologic pathways (*if* amyloid is

truly causal and *if* treatment is given when maximally effective, likely decades prior to clinical

symptoms) our results also suggest that it would be far from a panacea. Other pathologies clearly have

independent and substantial contributions to dementia risk, even in our sample where the vast majority

of cases were clinically diagnosed with AD and most had pathologic evidence of AD. These other

pathologies should be considered valid therapeutic targets. Given the hypothesized complex pathways

underlying dementia, a "one-size-fits-all" therapeutic strategy is unlikely to be successful. Drug

discovery work, including clinical trials, will face numerous challenges in identifying persons likely to

benefit from a given therapy, adequately powering studies to demonstrate benefit among this

subgroup, and managing toxicity and cost considerations for patients with evidence of multiple

pathologic processes.

AUTHOR CONTRIBUTIONS

MP, EM, AS, BJ, LY, NA, KB, LD, ML, YL, KN, LZ, AG, DM, KW, and JS contributed to the conception and design of the study; BJ, AG, MP, JS, KW, and LY contributed to the acquisition and analysis of the data; and BJ, EM, MP, AS, JS, and KW contributed to drafting the text or preparing figures.

CONFLICTS OF INTEREST

Nothing to report.

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FIGURE LEGENDS

Figure 1. Hypothesized pathways by which neuropathology may mediate the association of age and dementia.
Figure represents our *a priori* hypothesized model, with the addition of a modification allowing midtemporal tangles to contribute to the neocortical tangles latent variable. Squares or rectangles represent manifest variables and ellipses represent latent variables. Each single-headed arrow denotes a hypothesized unidirectional effect of one variable on another.

Abbreviations: Arter. Scler: arteriolosclerosis, CVDA: atherosclerosis, Gross: gross infarcts, Hippo. Sclerosis: hippocampal sclerosis; Mesio Tangles: Mesiotemporal tangles, Micro: microinfarcts, Neocort Tangles: neocortical neurofibrilary tangles, TDP: TAR DNA-binding protein 43, T-EC: neurofibrillary tangles in the entorhinal cortex, T-Hip: neurofibrillary tangles in the hippocampus, T-IP: neurofibrillary tangles in the inferior parietal cortex, T-MF: neurofibrillary tangles in the midfrontal cortex, T-MT: neurofibrillary tangles in the midtemporal cortex.

Figure 2. Results of path analysis considering mediation by the vascular pathology pathway of the effect of age on dementia risk.
Squares or rectangles represent manifest variables and ellipses represent latent variables. Each single-headed arrow denotes a hypothesized unidirectional effect of one variable on another. Numbers associated with effects are standardized regression coefficients (e.g., from age to dementia) or standardized factor loadings (i.e., from a latent variable to its indicators). Paths that were statistically significant at p<0.05 are represented by solid lines. Paths that were hypothesized but were not statistically significant at p<0.05 are denoted by dashed lines.
Abbreviations: Arter. Scler: arteriolosclerosis, CVDA: atherosclerosis (cerebrovascular disease of the artery), Gross: gross infarcts, Micro: microinfarcts.

Figure 3. Results of path analysis considering mediation by the amyloid/tau pathway of the effect of age on dementia risk.
Squares or rectangles represent manifest variables and ellipses represent latent variables. Each single-headed arrow denotes a hypothesized unidirectional effect of one variable on another. Numbers associated with effects are standardized regression coefficients (e.g., from age to dementia) or standardized factor loadings (i.e., from a latent variable to its indicators). Paths that were statistically significant at $p<0.05$ are represented by solid lines. Paths that were hypothesized but were not statistically significant at $p<0.05$ are denoted by dashed lines.
Abbreviations:, Neocort Tangles: neocortical neurofibrilary tangles, T-EC: neurofibrillary tangles in the entorhinal cortex, T-Hip: neurofibrillary tangles in the hippocampus, T-IP: neurofibrillary tangles in the inferior parietal cortex, T-MF: neurofibrillary tangles in the midfrontal cortex, T-MT: neurofibrillary tangles in the midtemporal cortex.

Figure 4. Results of path analysis considering mediation by the neocortical Lewy body pathology pathway of the effect of age on dementia risk.

Squares or rectangles represent manifest variables and ellipses represent latent variables. Each single-headed arrow denotes a hypothesized unidirectional effect of one variable on another. Numbers associated with effects are standardized regression coefficients (e.g., from age to dementia) or standardized factor loadings (i.e., from a latent variable to its indicators). Paths that were statistically significant at p<0.05 are represented by solid lines. Paths that were hypothesized but were not statistically significant at p<0.05 are denoted by dashed lines.

Figure 5. Results of path analysis considering mediation by the TDP43/hippocampal sclerosis pathway of the effect of age on dementia risk.
Squares or rectangles represent manifest variables and ellipses represent latent variables. Each single-headed arrow denotes a hypothesized unidirectional effect of one variable on another. Numbers associated with effects are standardized regression coefficients (e.g., from age to dementia) or standardized factor loadings (i.e., from a latent variable to its indicators). Paths that were statistically significant at $p<0.05$ are represented by solid lines. Paths that were hypothesized but were not statistically significant at $p<0.05$ are denoted by dashed lines.
Abbreviations: Hippo. Sclerosis: hippocampal sclerosis; TDP: TAR DNA-binding protein 43.

Figure 6. Results of path analysis of combined pathologic pathways mediating the effect of age on dementia risk.

Squares or rectangles represent manifest variables and ellipses represent latent variables. Each single-headed arrow denotes a hypothesized unidirectional effect of one variable on another. Numbers associated with effects are standardized regression coefficients (e.g., from age to dementia) or standardized factor loadings (i.e., from a latent variable to its indicators). Paths that were statistically significant at $p<0.05$ are represented by solid lines. Paths that were hypothesized but were not statistically significant at $p<0.05$ are denoted by dashed lines.

Abbreviations: Arter. Scler: arteriolosclerosis, CAA: cerebral amyloid angiopathy; CVDA: atherosclerosis, Gross: gross infarcts, Hippo. Sclerosis: hippocampal sclerosis; Micro: microinfarcts; Mesio. Tangles: mesiotemporal neurofibrilary tangles; Neocort Tangles: neocortical neurofibrilary tangles, TDP: TAR DNA-binding protein 43, T-EC: neurofibrillary tangles in the entorhinal cortex, T-Hip: neurofibrillary tangles in the hippocampus, T-IP: neurofibrillary tangles in the inferior parietal cortex, T-MF: neurofibrillary tangles in the midfrontal cortex, T-MT: neurofibrillary tangles in the midtemporal cortex.

Table 1. Characteristics of the eligible sample overall and by dementia status at time of death

	Total	Clinical Dementia Diagnosis Prior to Death	No Clinical Dementia Prior to Death
N (%)	1362 (100%)	594 (44%)	768 (56%)
Age at death, mean (SD)	88.6 (6.7)	90.0 (6.2)	87.5 (6.9)
Born before 1915, n (%)	389 (29%)	212 (36%)	177 (23%)
Male, n (%)	462 (34%)	187 (31%)	275 (36%)
Black, n (%)	53 (4%)	23 (4%)	30 (4%)
Study, n (%)			
MAP	670 (49%)	268 (45%)	401 (52%)
ROS	675 (50%)	322 (54%)	353 (46%)
MARS	17 (1%)	4 (1%)	13 (2%)
Neuritic plaques, mean (SD)	0.8 (0.8)	1.2 (0.9)	0.6 (0.7)
Neurofibrillary tangles, mean (SD)			
Entorhinal cortex	24.1 (21.4)	29.6 (22.7)	19.9 (19.4)
Hippocampus	24.2 (28.0)	32.9 (31.2)	17.4 (23.1)
Midtemporal cortex	6.0 (12.0)	10.7 (15.5)	2.4 (6.4)
Inferior parietal cortex	2.6 (6.8)	4.8 (9.0)	0.9 (3.8)
Midfrontal cortex	2.1 (6.2)	4.1 (8.5)	0.7 (2.8)
Gross infarcts, n (%)			
0	884 (65%)	333 (56%)	551 (71%)
1	243 (18%)	116 (20%)	127 (17%)
≥2	233 (17%)	143 (24%)	90 (12%)
Microinfarcts, n (%)			
0	961 (71%)	392 (66%)	569 (74%)
1	244 (18%)	117 (20%)	127 (17%)
≥2	155 (11%)	83 (14%)	72 (9%)
Atherosclerosis, n (%)			
0 (none)	250 (18%)	82 (14%)	168 (22%)
1	632 (47%)	271 (46%)	361 (47%)
2	378 (28%)	181 (31%)	197 (26%)
3 (severe)	93 (7%)	56 (9%)	37 (5%)
Arteriolosclerosis, n(%)			
0 (none)	430 (32%)	154 (26%)	276 (36%)
1	462 (34%)	201 (34%)	261 (34%)
2	343 (25%)	163 (28%)	180 (24%)
3 (severe)	114 (8%)	71 (12%)	43 (6%)
CAA, mean (SD)	1.1 (1.1)	1.4 (1.1)	0.9 (1.0)

Neocortical Lewy bodies, n (%)	167 (12%)	114 (19%)	53 (7%	
Hippocampal sclerosis, n (%)	119 (9%)	94 (16%)	25 (3%)	
TDP-43, mean (SD)	0.6 (1.0)	0.4 (0.7)	1.0 (1.2)	

Abbreviations: CAA, cerebral amyloid angiopathy; MAP, Memory and Aging Project; MARS, Minority Aging Research Study; ROS, Religious Orders Study; TDP-43, TAR DNA-binding protein 43

Table 2: Indices of Fit for Structural Models of Pathways Between Age and Dementia

Model	Description	Statistical index of fit			Practical indices of fit			
		χ^2	df	p	RMSEA [CI]	CFI	TLI	B_{age} (*SE*)
0	Age	0.00	0	--	.000 [.000, .000]	1.000	1.000	.24 (.03)
1	Vascular	2.97	5	.71	.000 [.000, .028]	1.000	1.011	.16 (.04)
2	Amyloid/tau hypothesized	105.83	16	<.0001	.064 [.053, .076]	.986	.968	.19 (.03)
2a	Amyloid/tau, modified	88.85	15	<.0001	.060 [.048, .072]	.988	.972	.21 (.03)
3	Lewy body hypothesized	101.53	1	<.0001	.272 [.228, .318]	.652	.000	.23 (.04)
3a	Lewy body, modified	0.00	0	--	.000 [.000, .000]	1.000	1.000	.21 (.03)
4	TDP / HS hypothesized	142.22	2	<.0001	.227 [.196, .2259]	.787	.000	.10 (.04)
4a	TDP / HS modified	2.16	1	.14	.029 [.000, .084]	.998	.982	.11 (.04)
5	All 4 pathways	139.35	79	<.001	.024 [.017, .030]	.993	.989	.01 (.04)
5a	All 4 pathways non-significant paths constrained to zero	132.17	84	<.001	.021 [.013, .027]	.994	.992	.01 (.04)

Note: *N* = 1362. For model names, HS = hippocampal sclerosis, and adjusted indicates that a direct effect of neuritic plaques on dementia was added to the a priori model. B_{age} (*SE*) = standardized regression coefficient (with standard error in parentheses) when predicting dementia from age.