Published in final edited form as:

Arch Psychiatr Nurs. 2014 June ; 28(3): 187–192. doi:10.1016/j.apnu.2014.01.004.

Gender Differences in Factors Associated with Delirium Severity in Older Adults with Dementia

Ann M. Kolanowski, PhD, RN, FAAN¹, Nikki L. Hill, PhD, RN¹, Esra Kurum, PhD², Donna M. Fick, PhD, RN, FAAN¹, Andrea M. Yevchak, PhD, RN³, Paula Mulhall, RPN, RGN, RN¹, Linda Clare, PhD⁴, and Michael Valenzuela, PhD⁵

Ann M. Kolanowski: amk20@psu.edu; Nikki L. Hill: Nln101@psu.edu; Esra Kurum: esrakurum@gmail.com; Donna M. Fick: dmf21@psu.edu; Andrea M. Yevchak: yevchaka@duq.edu; Paula Mulhall: pmk9@psu.edu; Linda Clare: l.clare@bangor.ac.uk; Michael Valenzuela: michael.valenzuela@sydney.edu.au

¹The Pennsylvania State University, College of Nursing, University Park, PA, USA

²Istanbul Medeniyet University, Istanbul, Turkey

³Duquesne University, School of Nursing, Pittsburgh, PA, USA

⁴Bangor University, School of Psychology, Gwynedd, UK

⁵Regenerative Neuroscience Group, Brain and Mind Research Institute, University of Sydney, Sydney, Australia

Abstract

The purpose of this descriptive correlational study was to explore potential gender differences in the relationship of dementia severity, age, APOE status, cognitive reserve and co-morbidity, (two potentially modifiable factors), to delirium severity in older adults. Baseline data from an ongoing clinical trial and a Poisson regression procedure were used in the analyses. Participants were 148 elderly individuals with dementia and delirium admitted to post-acute care. In women, delirium severity was related to dementia severity ($p=0.002$) and co-morbidity moderated that effect ($p=0.03$). In men, education was marginally associated with delirium severity ($p=0.06$). Implications for research are discussed.

Keywords

dementia; delirium; co-morbidity; cognitive reserve

© 2014 Elsevier Inc. All rights reserved.

Ann M. Kolanowski: 814-863-9901; Nikki L. Hill: 814-867-3265; Esra Kurum: +0216-280 33 33; Donna M. Fick: 814-865-9325; Andrea M. Yevchak: 412-396-6543; Paula Mulhall: 814-867-4656; Linda Clare: +44 (0) 1248 388178; Michael Valenzuela: +61 2 9114 4135

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Older adults with dementia have the highest risk for delirium, a neurobehavioral syndrome caused by acute physiological and/or psychological insults and characterized by an abrupt decline in cognitive function (Inouye, 2006). Delirium is prevalent in older adults with dementia: up to 89% experience delirium when hospitalized (Fick, Agostini, & Inouye, 2002). Delirium also carries a high rate of mortality: between 24 and 76% die within one year of the index episode (McCusker, Cole, Dendukuri, Han, & Belzile, 2003).

Beyond increased mortality, delirium has a major impact on other clinical and cost outcomes because it often persists beyond the acute phase of an illness. For example, two thirds of older adults admitted to post-acute (rehabilitation) care have delirium symptoms on admission (Kiely et al., 2003). Unresolved delirium in the post-acute phase of an illness prolongs rehabilitation because the associated cognitive decline interferes with the ability to fully engage in restorative therapies and increases the risk for permanent institutionalization (Fong et al., 2009). In addition to these poor health outcomes, delirium costs the U.S. healthcare system a staggering \$152 billion annually (Leslie, Marcantonio, Zhang, Leo-Summers, & Inouye, 2008).

It may be difficult to prevent delirium in older adults with dementia due to their underlying brain vulnerability (Marcantonio, Flacker, Wright, & Resnick, 2001). The need for evidence based treatment strategies that reduce the severity of delirium in people with dementia is critical and rests on a more informed understanding of etiology and associated risk factors.

Currently we do not know what biological and environmental factors increase delirium severity in people with dementia. Data indicate that delirium and dementia share many clinical, metabolic and cellular manifestations that indicate heightened brain vulnerability (Inouye & Ferrucci, 2006). Other data demonstrate gender differences in the clinical manifestation and outcome of dementia (Barnes et al., 2005). Additionally, males may have had a historical advantage with respect to building cognitive reserve against brain vulnerability, i.e., greater education and occupational achievement (Valenzuela et. al, 2013). Given the close relationship of delirium and dementia and the gender differences in dementia manifestation and outcome, we anticipated that there may be important gender differences in risk factors for greater delirium severity. The Institute of Medicine has argued for examination of gender differences in clinical research (National Research Council, 2001). Thus, the purpose of this descriptive correlational study was to explore a gap in knowledge about the potential gender differences in the relationship of dementia severity, age, apolipoprotein E (APOE) status, as well as cognitive reserve and co-morbidity, (two potentially modifiable factors), to delirium severity in older adults.

Review of the Literature

Non-modifiable Factors Related To Delirium

There are likely multiple neurobiological mechanisms contributing to delirium, and currently the neurotransmitter imbalance and the inflammatory hypotheses are the most prominent (Maldonado, 2013). The apolipoprotein E (APOE) gene, located on chromosome

19, has been associated with cognitive decline (Ertekin-Taner, 2007). A recent review of biomarkers for delirium found that most, but not all, of the six studies evaluated supported a role for APOE in the development of delirium (Khan, Zawahiri, Campbell, & Boustani, 2011). Though findings have not always been consistent (van Munster, Korevaar, de Rooij, Levi, & Zwinderman, 2007), the weight of the evidence indicates that having at least one copy of the e4 allele is associated with an increased risk of delirium in young and older adults as well as a more protracted course, independent of demographic and clinical covariates or premorbid cognitive impairments (Adamis et al., 2007).

Dementia is arguably the strongest risk factor for delirium (Cole, 2004; Miller & Ely, 2006). For example, in their observational study of 330 older adults admitted to a medical unit of a general hospital, Margiotta, Bianchetti, Ranieri and Trabucchi (2006) found that patients with pre-existing dementia were vulnerable to delirium at low levels of medical acuity than dementia-free patients. Moreover, the risk for delirium becomes greater as dementia severity increases (Voyer, McCusker, Cole, & Khomenko, 2006). Voyer and colleagues (2009) also found that advancing age increased risk for delirium in persons with dementia.

It may be difficult to prevent delirium in older adults with dementia due to their underlying brain vulnerability and risk profile (Marcantonio et al., 2001), so the identification of modifiable factors that influence delirium severity would be advantageous for this population. This knowledge could be used to inform the development of strategies, tailored to gender, that reduce the severity of delirium as well as the high cost and poor health outcomes that are associated with it.

Modifiable Factors and Relationship to Gender

Cognitive reserve is a theoretical concept used to explain why some people cope better than others with brain pathology (Tucker & Stern, 2011). An active cognitive lifestyle, involving lifelong participation in mentally stimulating educational, occupational and leisure activities, is thought to be a key contributor to building up such reserve (Bennett et al., 2003; Stern, 2012; Tucker & Stern, 2011). Much of the evidence in support of the cognitive reserve hypothesis has been in the area of risk for age-associated cognitive decline and dementia (Valenzuela & Sachdev, 2006). Older adults who engaged in mentally stimulating activities showed less than half the hippocampal volume decline over a three year period compared to those who engaged in fewer activities (Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008).

There is some evidence that cognitive reserve may also play a role in delirium. Jones and colleagues (2006) reported that level of education was significantly lower in patients who developed delirium during hospitalization compared to those who did not develop it. Further, leisure activity participation prior to hospitalization mediated the effect of education on delirium incidence, with physical activity exerting the greatest effect (Yang et al., 2008).

The cognitive benefits of mentally stimulating activities are evident when participation in mentally stimulating activities is a lifetime pattern as well as when they are initiated for the first time in late life (Leung et al., 2011). While educational level has been associated with incidence of delirium, the contribution of late-life cognitive lifestyle to delirium severity has not been studied in older adults with dementia. Because women tend to have a more active

late life cognitive lifestyle than men (Valenzuela et al., 2013), but men in this historical cohort enjoyed greater educational opportunities than women, we explored gender differences in the effects of cognitive reserve on delirium severity.

Multiple co-morbidities have the potential to initiate a cascade of negative health outcomes. The loss of physiological reserves brought on by multiple diseases predicts vulnerability to diminished homeostatic capacity (Quinlan et al., 2011). The existing evidence indicates that comorbidity and frailty are distinct but related entities that manifest complex interactions which signal a state of vulnerability to physical and cognitive stressors, and thus, increase the risk of delirium during acute illnesses. Because men with dementia carry a higher burden of co-morbidity than women (Buchanan, Wang, Ju, & Graber, 2004) we explored gender differences in the association of co-morbidity with delirium severity.

Methods

Data from the baseline period of an ongoing clinical trial were used to address the aim of this project. In the parent study, cognitively stimulating activities are being tested for their efficacy in resolving delirium in older adults with dementia. The protocol has been published and received approval from the university Institutional Review Board (*Blinded for review*).

In the trial, subjects are recruited at admission to post-acute care following a hospitalization. Eight community-based skilled nursing facilities in central and northeast Pennsylvania serve as recruitment sites. All subjects have a diagnosis of dementia and delirium. Dementia is established based on a score of three or greater on the Modified Blessed Dementia Rating Scale (MBDRS) with symptoms evident for at least six months duration (Blessed, Tomlinson, & Roth, 1968), and a Clinical Dementia Rating (CDR) score of from 0.5 to 2.0, indicating mild to moderate stage dementia (Hughes, Berg, Danziger, Coben, & Martin, 1982). Presence of delirium is established by positive findings on the Confusion Assessment Method (CAM; Inouye et al., 1990), a standardized diagnostic algorithm for delirium allowing persons without formal psychiatric training to quickly and accurately identify delirium. The CAM has been validated in persons with dementia, but because of the risk of feature overlap with dementia, we take a conservative approach and include only subjects with full (three or more features) or sub-syndromal (two features) delirium. A panel of three experts in dementia (neuropsychologist, neurologist and geriatrician) adjudicates all dementia and delirium diagnoses.

Other inclusion criteria include: age 65 years or older; English speaking; community-residing prior to most recent hospitalization; and having a legally authorized representative (usually a spouse or adult child) who provides medical history, education, occupation and leisure data. These individuals meet criteria specified by Ritchie and Fuhrer (1996) for knowledgeable informants, i.e., monthly contact with the subject for ten years during the subject's adult life prior to the dementia diagnosis. Subject exclusion criteria include: having any neurological condition associated with cognitive impairment other than dementia, including Parkinson's disease with Lewy Body dementia, Huntington's disease, normal pressure hydrocephalus, seizure disorder, subdural hematoma, head trauma, or known

structural brain abnormalities; nonverbal; having a life expectancy of six months or less; acute major depression; acute psychiatric condition; stroke; and severe hearing and vision impairment. Individuals who meet enrollment criteria are invited to participate in the trial.

Following written consent from the participant's legally authorized representative, demographic variables, medical history, a comprehensive assessment of cognitive reserve (education and cognitive lifestyle), and APOE genotype are obtained at baseline by trained research assistants. We report findings for the first 148 participants with complete data who have been enrolled in the trial.

Measures

Demographics and dementia severity—Age, gender, race and dementia severity were obtained using a medical chart review and a face-to-face or phone interview with the participant's legally authorized representative. The CDR scale (described above) was used to determine dementia severity.

APOE status—APOE genotype was determined by extracting DNA from buccal swabs using a protocol optimized by the Institute of Psychiatry in London (Freeman et al., 2003). To identify the six APOE genotypes comprising the APOE e2, e3 and e4 alleles, two single nucleotide polymorphisms (SNPs) are assayed using the TaqMan Allele Discrimination method.

Cognitive reserve—Assessment of participants' cognitive lifestyle, a proxy measure for cognitive reserve, was obtained by interviewing the legally authorized representative using the *Lifetime of Experiences Questionnaire* (LEQ) a reliable and valid instrument for assessing educational, occupational, and leisure lifestyle activities that are protective against cognitive decline (Valenzeula & Sachdev, 2007). The LEQ consists of 42 items constructed around two dimensions: three life stages (young, mid, and late adulthood) and specific vs. non-specific mental activity in each stage. Activities that contribute to specific scores for each stage are education, occupational attainment and social engagement for young, mid and late adulthood respectively. Non-specific activities for each stage include travel, physical activity and engagement with family and friends. Specific and non-specific scores are combined for each stage and then summed for a total LEQ score. Higher scores indicate higher lifetime mental activity. The LEQ has an overall internal consistency of .66, test-retest reliability of .98 and discriminates well between older adults with high and low mental activity levels.

For this study we used data from two sub-scales: the young adulthood (education level only) and the total score for the late adulthood stage because our informants were spouses or adult children of the participant and may not have had knowledge of the participant's earlier life experiences other than educational attainment and late life activity. Education scores are additive based on years of education, including post-secondary and specialized education, and weighted according to the level of education (i.e., doctoral education is more highly weighted than undergraduate education). Education is scored as: zero for up to 7 years of education; four for 8 to 10 years; eight for 11 to 12 years; nine and above for post-secondary

education, including any fraction of post-secondary programs completed. Scores can range from zero to 37.5. The late life total score can range from 3 to 63.

Comorbidity—The Charlson Comorbidity Index (van Doorn et al., 2001) is a weighted index that takes into account the number and seriousness of 17 co-morbid diseases. The co-morbidity score for each subject is calculated by summing the weighted diseases. Because all participants in this study had dementia, we did not include that disease in our calculation, so the index score for our sample reflects co-morbidity over and above that accounted for by the dementia diagnosis.

Delirium Severity—Delirium severity was measured using two instruments: 1) the Mini Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975), a 30-item cognitive screen, and 2) the Confusion Assessment Method (CAM) (Inouye et al., 1990). The severity score was calculated using a method developed by Inouye and colleagues (1999). Using both the CAM and MMSE results we summed the responses to the following items: CAM fluctuating course item (0–1); MMSE attention item (0–5); and CAM level of consciousness item (0–2). Total scores can range from one to eight with higher scores indicating greater delirium severity.

Analysis

Descriptive statistics for each quantitative outcome by gender were calculated. First we explored the association among all the variables, that is, age, educational level, CDR, Charlson comorbidity score, late life LEQ score, APOE status and delirium severity. Since none of the variables were normally distributed, we employed Kendall's rank correlation coefficient along with tau test, which does not require the relationship between variables to be linear and is less sensitive to non-normality than Pearson's correlation coefficient. We suspected that some of the demographic and clinical characteristics might differ between genders. In order to investigate this, we conducted Wilcoxon rank sum test for quantitative variables, that is, age, educational level, CDR, Charlson-comorbidity score, late life LEQ score, delirium severity, and Fisher's exact test for the qualitative variable, that is, APOE status.

Our main interest was investigating the relationship between delirium severity and other study variables for each gender. Thus, for each gender, a regression model was fit to test the significance of each variable on delirium severity. In our model, we also included interaction terms between each study variable. Ignoring an interaction may cause serious interpretation problems, since an interaction being significant indicates that the effect of either of these variables on delirium severity depends on the other variable; interpreting only the main effects of these variables would be incorrect. In our regression models, a Poisson regression procedure was employed since the delirium severity score is discrete and approximately equidispersed, that is, the variance of this score is approximately equal to its mean. A significance level of 0.05 was used in all the tests.

Results

Table 1 lists the demographic and clinical characteristics of the entire sample and by gender. Overall, participants were primarily of advanced age, female, and Caucasian. On average, they had a high school education with some post-secondary education. Participants had a mean CDR of 1.2 (± 0.6) indicating a mild stage of dementia and approximately 2 additional co-morbidities beyond their dementia diagnosis. Over 30% of the participants were positive for at least one APOE e4 allele and this compares to 15% found in the general population (Ertekin-Taner, 2007). The mean delirium severity score was 4.8 (± 1.8) and scores can range from 0–8.

The results by gender indicate that the mean educational level, dementia severity, co-morbidity and delirium severity scores were higher for males than for females. In females, the mean late life LEQ score was greater than that of males. However, only age reached statistical significance with women being older than men ($p=0.04$).

For the sample as a whole, dementia severity (CDR) was significantly related to delirium severity ($r=0.208$; $p=0.002$). Education and delirium severity were marginally and negatively associated ($r=-0.123$; $p=0.058$). The relationship between age and late life LEQ ($r=0.148$; $p=0.009$) and education and late life LEQ ($r=0.121$; $p=0.04$) were both statistically significant. No other significant relationships were found between any of the study variables.

Our main interest was in observing for different trends that might exist for each gender. In the regression model for females, we found that dementia severity was positively and significantly related to delirium severity ($z\text{-value}=3.303$ and $p=0.002$). The estimate of the regression coefficient for this effect was found to be 0.422 with a standard error of 0.128; hence, the 95% confidence interval for the regression coefficient is (0.166, 0.678). We also found a significant interaction of dementia severity with co-morbidity ($z\text{-value}=-2.282$ and $p=0.033$). The regression coefficient for this interaction term is estimated as -0.150 with a standard error of 0.066. Therefore, the 95% confidence interval for the regression coefficient is (-0.282 , -0.018). Figure 1 illustrates this interaction in which, for most levels of dementia severity, as co-morbidity increased the severity of delirium also increased. More specifically, when the co-morbidity score is zero, one, or two, delirium severity increases as the dementia severity increases, whereas when the co-morbidity score is four, delirium severity only increases when dementia severity increases from one to two. Note that we only had one female subject for both of the co-morbidity scores five and six; hence, they are omitted in Figure 1.

For males, the regression model indicated that education was negatively and marginally related to delirium severity, such that as educational level went up, delirium became less severe ($z\text{-value}=-1.868$ and $p=0.062$). We did not find any significant interactions for any of our study variables in the model for male participants.

Discussion

The purpose of this exploratory study was to examine gender differences in the relationship of dementia severity, age, APOE status, and cognitive reserve and co-morbidity, two potentially modifiable risk factors, to delirium severity in older adults admitted to post-acute care. For women, greater dementia severity and higher co-morbidity were found to increase delirium severity. We anticipated these findings based on prior research that indicates a relationship between dementia and delirium (Cole, 2004; Miller & Ely, 2006) and also the effect of multiple co-morbidities on increased vulnerability to cognitive and physical stressors such as those that might precipitate delirium (Quinlan et al., 2011). Improved understanding of the interaction between dementia and delirium severity from this study will be critical to furthering our understanding of the shared neuropathology and clinical impact of delirium and dementia. The effect of increasing co-morbidity on delirium severity in this sample was stronger in women than in men. This finding supports work indicating that older women with dementia experience greater disability/frailty than men, despite having less co-morbidity (Buchanan et al., 2004; Sinforiani et al., 2010).

Co-morbidity may impact vulnerability to delirium at lower levels in women than men and the pathway may be through frailty. A recent discussion in the literature indicates that frailty and delirium overlap clinically, have similar pathophysiology, and that frailty increases risk for delirium (Quinlan et al., 2011). Our findings, although very preliminary, suggest that older women with dementia, more so than their male counterparts, may gain resistance to greater delirium severity through efforts that improve physical health and prevent high co-morbidity and resultant frailty. Others have found that by attending to mobilization and rehabilitation, delirium can resolve, including in people with dementia (Bee Gek Tay, Chew Chan, & Sian Chong, 2013). We recommend that future studies of gender differences in delirium predictors include measures of frailty in addition to co-morbidity given recent findings that support a close association between these constructs.

For men, unlike for women, delirium severity was greater in those with less education. Education has historically been a proxy for cognitive reserve and our male participants had a greater range of education than women. Education, and other mentally stimulating activity, is thought to build reserve both by increasing synaptic connections and density as well as by developing the ability to use alternate strategies for circumventing brain pathology. Men might be more resistant to brain pathology because they have more cognitive reserve than women. In a recent PET study, males with dementia had a greater reduction in cerebral metabolism than would be predicted based on their higher clinical function (Perneczky, Drzezga, Diehl-Schmid, Li, & Kurz, 2007). Barnes and colleagues (2005) also report that dementia pathology is more likely to be clinically expressed in women than men. These findings may be due to the larger brain size and greater number and density of neurons in men than women or in their ability to use compensatory mechanisms in the face of brain pathology. In light of this literature, older men with dementia in our sample, more so than their female counterparts, may have gained greater resistance to increasing delirium severity through an interaction of their potentially larger brain size and efforts that promoted their cognitive reserve in young adulthood, i.e. their education.

We found no effect for late life cognitive lifestyle on delirium severity in either gender. In this sample of cognitively impaired older adults, late life cognitive lifestyle was much less enriched than that found in a population-based sample of cognitively intact older adults (Valenzuela et al., 2013). This is understandable as the late life period is likely when the dementia process would have affected our participants' ability to engage in many of the cognitive reserve building activities captured by the LEQ, such as joining social groups, attending concerts, reading and traveling. We did not collect data on age at dementia diagnosis which may have helped clarify the association of late life cognitive reserve and delirium severity. This is a limitation of the study.

Regardless of our findings, there are data to support the advantage of building cognitive reserve across the entire life course in both genders. Engagement in complex cognitive activities in mid- and late life can offer important benefits (Martin, Clare, Altgassen, Cameron, & Zehnder, 2011) and can help to improve function in those with established dementia (Clare et al., 2010). Cognitive reserve is built from multiple sources and changes across the life course depending on environmental opportunities and behavior (Stern, 2012). In addition, preliminary data suggest that mentally stimulating activities may reduce the severity and duration of delirium in older adults with dementia (Kolanowski et al., 2011). Future studies should examine cognitive reserve across the entire life span. In that respect, there is a need to develop instruments that reliably capture this construct when informants provide these data, as was the case in the current study.

APOE status did not associate with delirium severity in either gender. We note that not all studies have found a positive relationship (i.e., van Munster et al., 2007) although most have demonstrated a role for this genetic marker in delirium. In the van Munster study there was a significant correlation between APOE status and delirium but only in patients below 75 years of age. Our sample had a mean age of 84.9 years, and it is possible that APOE status may not be as critical a factor for predicting delirium severity in late life as in younger ages. It may also be that faster recovery from, rather than severity of delirium, is associated with APOE status in cognitively impaired older populations (Adamis et al., 2007; Ely et al., 2007). We do not fully understand the multiple neurobiological mechanisms contributing to delirium or the contribution of this genetic marker to delirium severity in older adults with dementia.

As expected, and for the sample as a whole, we found that older adults in later stages of dementia had greater severity of delirium compared to those in earlier stages of dementia. This has been reported in a number of prior studies and likely reflects the effects of progressive dementia pathology on brain vulnerability to noxious stimuli. All of our participants were admitted to the study following a hospitalization where noxious environmental and medical insults could have precipitated the delirium episode.

Limitations of this study include the cross-sectional and secondary nature of the analysis and the lack of a comprehensive measure for informants that captures life span cognitive reserve. Also lacking was the date of initial dementia diagnosis. Despite these limitations, this exploratory study used data from an ongoing clinical trial and found important gender differences in factors associated with delirium severity that could be exploited to reduce its

severity in older adults with dementia. The identification of malleable targets that are associated with delirium severity is important for the design of interventions that are sensitive to gender differences and for the further development of current delirium guidelines (O'Mahony, Murthy, Akunne, & Young, 2011). Attention to reduction of co-morbidities and building cognitive reserve across the life span might be useful strategies to test in clinical trials aimed at improving mental health outcomes in this vulnerable population.

Acknowledgments

This work was supported by National Institute of Nursing Research grants [R01 NR012242] awarded to Ann Kolanowski and Donna Fick and [F31 NR013304] awarded to Nikki Hill. The authors' funding sources did not participate in the planning, collection, analysis or interpretation of data or in the decision to submit for publication.

Michael Valenzuela was supported by a National Health & Medical Research Council of Australia Clinical Career Development Fellowship (1004156).

References

- Adamis D, Treloar A, Martin FC, Gregson N, Hamilton G, Macdonald AJD. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. *International Journal of Geriatric Psychiatry*. 2007; 22(7):688–694.10.1002/gps.1732 [PubMed: 17203511]
- Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex Differences in the Clinical Manifestations of Alzheimer disease Pathology. *Archives of General Psychiatry*. 2005; 62(6):685–691.10.1001/archpsyc.62.6.685 [PubMed: 15939846]
- Bee Gek Tay L, Chew Chan MP, Sian Chong M. Functional improvement in hospitalized older adults is independent of dementia diagnosis: Experience of a specialized delirium management unit. *Journal of Hospital Medicine*. 2013; 8(6):321–327.10.1002/jhm.2035 [PubMed: 23553979]
- Bennett DA, Wilson RS, Schneider JA, Evans DA, Mendes de Leon CF, Arnold SE, Bienias JL. Education Modifies the Relation of AD Pathology to Level of Cognitive Function in Older Persons. *Neurology*. 2003; 60(12):1909–1915. [PubMed: 12821732]
- Blessed G, Tomlinson BE, Roth M. The Association between Quantitative Measures of Dementia and of Senile Change in the Cerebral Grey Matter of Elderly Subjects. *British Journal of Psychiatry*. 1968; 114(512):797–811. [PubMed: 5662937]
- Buchanan RJ, Wang S, Ju H, Graber D. Analyses of Gender Differences in Profiles of Nursing Home Residents with Alzheimer's disease. *Gender Medicine*. 2004; 1(1):48–59. doi: [http://dx.doi.org/10.1016/S1550-8579\(04\)80010-X](http://dx.doi.org/10.1016/S1550-8579(04)80010-X). [PubMed: 16115583]
- Clare L, Linden DEJ, Woods RT, Whitaker R, Evans SJ, Parkinson CH, Rugg MD. Goal-oriented cognitive rehabilitation for people with early-stage Alzheimer disease: a single-blind randomized controlled trial of clinical efficacy. *The American Journal of Geriatric Psychiatry*. 2010; 18(10):928–939.10.1097/JGP.0b013e3181d5792a [PubMed: 20808145]
- Cole MG. Delirium in elderly patients. *The American Journal of Geriatric Psychiatry*. 2004; 12(1):7–21. [PubMed: 14729554]
- Ely EW, Girard TD, Shintani AK, Jackson JC, Gordon SM, Thomason JWW, Laskowitz DT. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. *Critical Care Medicine*. 2007; 35(1):112–117. 10.1097/1001.CCM.0000251925.0000218961.CA. [PubMed: 17133176]
- Ertekin-Taner N. Genetics of Alzheimer's Disease: A Centennial Review. *Neurologic Clinics*. 2007; 25(3):611–667. doi: <http://dx.doi.org/10.1016/j.ncl.2007.03.009>. [PubMed: 17659183]
- Fick DM, Agostini JV, Inouye SK. Delirium Superimposed on Dementia: A Systematic Review. *Journal of the American Geriatrics Society*. 2002; 50(10):1723–1732.10.1046/j.1532-5415.2002.50468.x [PubMed: 12366629]

- Folstein MF, Folstein SE, McHugh PR. Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. 1975; 12(3):189–198. doi: [http://dx.doi.org/10.1016/0022-3956\(75\)90026-6](http://dx.doi.org/10.1016/0022-3956(75)90026-6). [PubMed: 1202204]
- Fong TG, Jones RN, Shi P, Marcantonio ER, Yal L, Rudolph JL, Inouye SK. Delirium Accelerates Cognitive Decline in Alzheimer disease. *Neurology*. 2009; 72(18):1570–1575.10.1212/WNL.0b013e3181a4129a [PubMed: 19414723]
- Freeman B, Smith N, Curtis C, Hockett L, Mill J, Craig IW. DNA from Buccal Swabs Recruited by Mail: Evaluation of Storage Effects on Long-Term Stability and Suitability for Multiplex Polymerase Chain Reaction Genotyping. *Behavior Genetics*. 2003; 33(1):67–72.10.1023/A:1021055617738 [PubMed: 12645823]
- Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A New Clinical Scale for the Staging of Dementia. *British Journal of Psychiatry*. 1982; 140:566–572. [PubMed: 7104545]
- Inouye SK. Delirium in Older Persons. *The New England Journal of Medicine*. 2006; 354(11):1157–1165.10.1056/NEJMr052321 [PubMed: 16540616]
- Inouye SK, Bogardus ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney LM. A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients. *The New England Journal of Medicine*. 1999; 340(9):669–676.10.1056/NEJM199903043400901 [PubMed: 10053175]
- Inouye SK, Ferrucci L. Introduction: Elucidating the Pathophysiology of Delirium and the Interrelationship of Delirium and Dementia. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2006; 61(12):1277–1280.
- Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying Confusion: The Confusion Assessment Method A New Method for Detection of Delirium. *Annals of Internal Medicine*. 1990; 113(12):941–948.10.7326/0003-4819-113-12-941 [PubMed: 2240918]
- Jones RN, Yang FM, Zhang Y, Kiely DK, Marcantonio ER, Inouye SK. Does Educational Attainment Contribute to Risk for Delirium? A Potential Role for Cognitive Reserve. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2006; 61(12):1307–1311.
- Khan BA, Zawahiri M, Campbell NL, Boustani MA. Biomarkers for Delirium—A Review. *Journal of the American Geriatrics Society*. 2011; 59:S256–S261.10.1111/j.1532-5415.2011.03702.x [PubMed: 22091570]
- Kiely DK, Bergmann MA, Murphy KM, Jones RN, Orav EJ, Marcantonio ER. Delirium Among Newly Admitted Postacute Facility Patients: Prevalence, Symptoms, and Severity. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2003; 58(5):M441–M445.10.1093/gerona/58.5.M441
- Kolanowski AM, Fick DM, Clare L, Steis MR, Boustani MA, Litaker M. Pilot study of a nonpharmacological intervention for delirium superimposed on dementia. *Research in Gerontological Nursing*. 2011; 4(3):161–167.10.3928/19404921-20101001-98 [PubMed: 21053841]
- Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. *Archives of Internal Medicine*. 2008; 168(1):27–32.10.1001/archinternmed.2007.4 [PubMed: 18195192]
- Leung GT, Fung AW, Tam CW, Lui VW, Chiu HF, Chan WM, Lam LC. Examining the association between late-life leisure activity participation and global cognitive decline in community-dwelling elderly Chinese in Hong Kong. *International Journal of Geriatric Psychiatry*. 2011; 26(1):39–47.10.1002/gps.2478 [PubMed: 21157849]
- Maldonado JR. Neuropathogenesis of Delirium: Review of Current Etiologic Theories and Common Pathways. *The American Journal of Geriatric Psychiatry*. 2013; 21(12):1190–1222. doi: <http://dx.doi.org/10.1016/j.jagp.2013.09.005>. [PubMed: 24206937]
- Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing Delirium After Hip Fracture: A Randomized Trial. *Journal of the American Geriatrics Society*. 2001; 49(5):516–522.10.1046/j.1532-5415.2001.49108.x [PubMed: 11380742]
- Margiotta A, Bianchetti A, Ranieri P, Trabucchi M. Clinical characteristics and risk factors of delirium in demented and not demented elderly medical inpatients. *The Journal of Nutrition, Health & Aging*. 2006; 10(6):535–539.

- Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. Cognition-based interventions for healthy older people and people with mild cognitive impairment. *Cochrane Database of Systematic Reviews*. 2011; (1):CD006220.10.1002/14651858.CD006220.pub2 [PubMed: 21249675]
- McCusker J, Cole MG, Dendukuri N, Han L, Belzile E. The course of delirium in older medical inpatients: a prospective study. *Journal of General Internal Medicine: JGIM*. 2003; 18(9):696–704.
- Miller RR, Ely EW. Delirium and cognitive dysfunction in the intensive care unit. *Seminars in Respiratory and Critical Care Medicine*. 2006; 27(3):210–220.10.1055/s-2006-945532 [PubMed: 16791755]
- National Research Council. Exploring the biological contributions to human health: does sex matter? *Journal of Women's Health & Gender-Based Medicine*. 2001; 10(5):433–439.10.1089/152460901300233902
- O'Mahony R, Murthy L, Akunne A, Young J. Synopsis of the National Institute for Health and Clinical Excellence Guideline for Prevention of Delirium. *Annals of Internal Medicine*. 2011; 154(11):746–751.10.7326/0003-4819-154-11-201106070-00006 [PubMed: 21646557]
- Perneczky R, Drzezga A, Diehl-Schmid J, Li Y, Kurz A. Gender differences in brain reserve. *Journal of Neurology*. 2007; 254(10):1395–1400.10.1007/s00415-007-0558-z [PubMed: 17934882]
- Quinlan N, Marcantonio ER, Inouye SK, Gill TM, Kamholz B, Rudolph JL. Vulnerability: The Crossroads of Frailty and Delirium. *Journal of the American Geriatrics Society*. 2011; 59:S262–S268.10.1111/j.1532-5415.2011.03674.x [PubMed: 22091571]
- Ritchie K, Fuhrer R. The validation of an informant screening test for irreversible cognitive decline in the elderly: performance characteristics within a general population sample. *International Journal of Geriatric Psychiatry*. 1996; 11(2):149–156.10.1002/(SICI)1099-1166(199602)11:2<149::AID-GPS298>3.0.CO;2-5
- Sinforiani E, Citterio A, Zucchella C, Bono G, Corbetta S, Merlo P, Mauri M. Impact of Gender Differences on the Outcome of Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders*. 2010; 30(2):147–154. doi: <http://dx.doi.org/10.1159/000318842>. [PubMed: 20733307]
- Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*. 2012; 11(11):1006–1012. doi: [http://dx.doi.org/10.1016/S1474-4422\(12\)70191-6](http://dx.doi.org/10.1016/S1474-4422(12)70191-6).
- Tucker AM, Stern Y. Cognitive Reserve in Aging. *Current Alzheimer Research*. 2011; 8(4):354–360. [PubMed: 21222591]
- Valenzuela MJ, Leon I, Suo C, Piamba DM, Kochan N, Brodaty H, Sachdev P. Cognitive Lifestyle in Older Persons: The Population-Based Sydney Memory and Ageing Study. *Journal of Alzheimer's Disease*. 2013; 36(1):87–97.10.3233/JAD-130143
- Valenzuela MJ, Sachdev P. Brain Reserve and Dementia: A Systematic Review. *Psychological Medicine*. 2006; 36(04):441–454.10.1017/S0033291705006264 [PubMed: 16207391]
- Valenzuela MJ, Sachdev P. Assessment of complex mental activity across the lifespan: development of the Lifetime of Experiences Questionnaire (LEQ). *Psychological Medicine*. 2007; 37(7):1015–1025.10.1017/S003329170600938X [PubMed: 17112402]
- Valenzuela MJ, Sachdev P, Wen W, Chen X, Brodaty H. Lifespan Mental Activity Predicts Diminished Rate of Hippocampal Atrophy. *PLoS ONE*. 2008; 3(7):e2598.10.1371/journal.pone.0002598 [PubMed: 18612379]
- van Doorn C, Bogardus ST, Williams CS, Concato J, Towle VR, Inouye SK. Risk adjustment for older hospitalized persons: A comparison of two methods of data collection for the Charlson index. *Journal of Clinical Epidemiology*. 2001; 54(7):694–701. doi: [http://dx.doi.org/10.1016/S0895-4356\(00\)00367-X](http://dx.doi.org/10.1016/S0895-4356(00)00367-X). [PubMed: 11438410]
- van Munster BC, Korevaar JC, de Rooij SE, Levi M, Zwinderman AH. The association between delirium and the apolipoprotein E epsilon4 allele in the elderly. *Psychiatric Genetics*. 2007; 17(5):261–266.10.1097/YPG.0b013e3280c8efd4 [PubMed: 17728664]
- Voyer P, McCusker J, Cole MG, Khomenko L. Influence of prior cognitive impairment on the severity of delirium symptoms among older patients. *The Journal of Neuroscience Nursing*. 2006; 38(2):90–101. [PubMed: 16681289]

- Voyer P, Richard S, Doucet L, Carmichael PH. Predisposing Factors Associated With Delirium Among Demented Long-Term Care Residents. *Clinical Nursing Research*. 2009; 18(2):153–171.10.1177/1054773809333434 [PubMed: 19377042]
- Yang FM, Inouye SK, Fearing MA, Kiely DK, Marcantonio ER, Jones RN. Participation in Activity and Risk for Incident Delirium. *Journal of the American Geriatrics Society*. 2008; 56(8):1479–1484.10.1111/j.1532-5415.2008.01792.x [PubMed: 18547359]

Figure 1.
Interaction Effect of Co-morbidity and Dementia Severity on Delirium Severity.

Table 1

Means and SD for Demographic and Clinical Characteristics by Gender and for Total Sample

Variable	Males N=59	Females N= 89	Total N=148
Age	83.7(±6.6)	85.8(±6.7)	84.9(±6.7)
Education *	11.4(±8.5)	8.6(±4.9)	9.8(±6.7)
APOE ** n(%) positive e4	18(30.5)	29(32.6)	47(31.7)
Late life LEQ ***	18.5(±4.9)	19.9(±5.1)	19.4(±5.0)
Charleson ^	2.0(±1.6)	1.6(±1.3)	1.8(±1.5)
CDR ^^	1.2(±0.6)	1.2(±0.6)	1.2(±0.6)
DeliriumSeverity ^^^	5.0(±1.8)	4.7(±1.9)	4.8(±1.8)

* Education score= 0 = 7 years of education; 4= 8 to 10 years; 8 = 11 to 12 years; 9 and 10 = post secondary education, including any fraction of post secondary programs completed. Range= 0 to 37.5

** Apolipoprotein E (APOE) n(%)- number and percentage of participants with one or two e4 alleles

*** Late Life *Lifetime of Experiences Questionnaire* (LEQ)- scores can range from 3 to 63.

^ Charleson Co-morbidity Index- scores can range from 0 to 33 (includes dementia)

^^ Clinical Dementia Rating (CDR) scale- scores range from 0.5 to 2.0

^^^ Delirium Severity- scores can range from 0 to 8.