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

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A B S T R A C T

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.

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 1 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

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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, Richard, Doucet, and Carmichael (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 3 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 et al. (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 6 months duration (Blessed, Tomlinson, & Roth, 1968), and a Clinical Dementia Rating (CDR) score 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 10 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 6 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.

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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 (Valenzuela & 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 et al. (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

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)c	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)
Delirium severity^^^	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 ≥ 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.

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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 ranged 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-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-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). Fig. 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 Fig. 1.

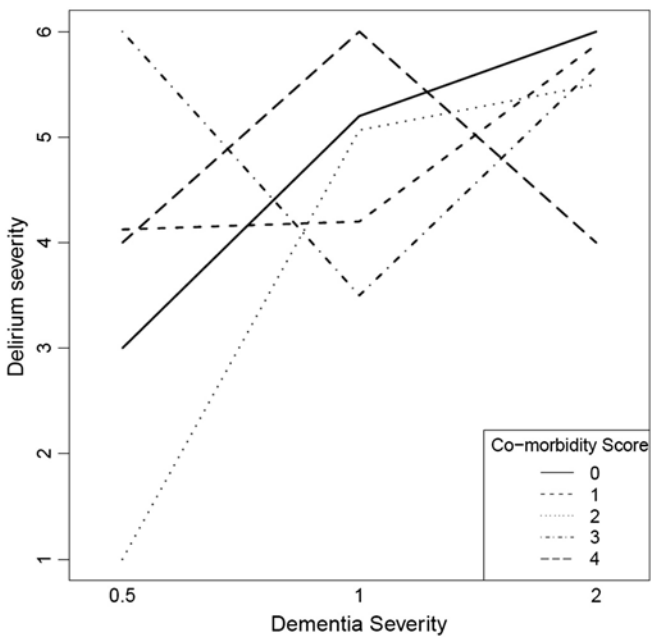

Fig. 1. Interaction effect of co-morbidity and dementia severity on delirium severity.

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-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 et al. (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

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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 demonstated 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.

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