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Towards prevention of mild cognitive impairment in older adults with depression: an observational study of potentially modifiable risk factors.

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Abstract

Objective: Late life depression has been associated with increased risk of mild cognitive impairment (MCI) and dementia. Predictors of increased risk are incompletely understood. Identification of potentially modifiable risk factors could facilitate prevention of MCI and dementia. We aim to determine which clinical characteristics are associated with increased risk of MCI among older adults with depression and normal cognition at baseline.

Methods: Using data from the National Alzheimer's Coordinating Centre study participants with normal cognition and a history of clinically defined depression were followed until first diagnosis of MCI or dementia (where MCI was not diagnosed).

Results: 2655 study participants were followed for median duration of 41.8 months. 586 (22.1%) developed either MCI (n = 509, 19.2%) or dementia (n = 77, 2.9%). In survival analyses cognitive decline was associated with age, sex, education, baseline cognition & several potentially modifiable risk factors including: vascular risk factors, hearing impairment, B12 deficiency, active depression within the last 2 years and increased severity of depression. In an adjusted survival analysis (HR, 95% CI), only age (1.07, 1.05 – 1.08), female sex (0.72, 0.59 – 0.88), education (0.96, 0.93 – 0.99), baseline cognition (0.87, 0.82 – 0.93), active depression within the last 2 years (1.41, 1.15 – 1.74) & increased severity of depression (1.05, 1.02 – 1.09) remained significantly associated with development of MCI or dementia.

Conclusion: Development of MCI is associated with several potentially modifiable risk factors in older adults with depression. Future studies should determine whether active management of risk factors could reduce incidence of MCI in this vulnerable population.

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Conflicts of Interest:

NH has received consultation fees from Pfizer, Lilly, Merck & Astellas. KL has received grant support from AbbVie, Axovant & advisory board fees from Lundbeck, Otsuka & Novartis. DG and AK have no conflicts to declare.

Keywords

Depression; cognition; mild cognitive impairment

Introduction

Depression in later life has been associated with a two-fold increased risk of dementia. Research efforts to prevent or delay onset of dementia have focused upon individuals with Mild cognitive impairment (MCI) known to be at high-risk of progression to dementia. In observational studies approximately 39% of those diagnosed with MCI in specialist settings, and 22% from general population studies, will progress to dementia over the following 3 to 10 years. Depression has been associated with accelerated cognitive decline and in a previous analysis of older adults with depression and MCI attending specialist services we found that approximately 40% developed Alzheimer's dementia over a median follow up duration of only 27 months. Cognitive decline in depression is associated with persistence of symptoms and treatment resistance.¹ The high rate of progression to dementia in older adults with depression and MCI necessitates a greater focus upon *prevention of MCI* if we are to substantially reduce the incidence of dementia in older adults with depression and potentially improve illness course.

Comparatively fewer studies have examined the rate of progression from normal cognition to MCI among older adults with depression. In studies that have examined this question there have been variable findings likely reflecting differences in clinical populations and diagnostic criteria. In one population study of older adults with moderate or high depressive symptoms and normal cognition at baseline approximately 20% developed MCI over 6 years while another population study documented new onset MCI in 13.3% of depressed participants after 2.6 years of follow up. Higher rates have been reported in clinical samples, with 23% of older adults with depression and normal cognition at baseline developing cognitive impairment after a year of follow up in one analysis.

Predictors of cognitive decline and potentially modifiable risk factors for cognitive decline remain incompletely understood in adults with depression. Vascular risk factors are known to be associated with cognitive decline in the general population and are particularly prevalent in older adults with depression. Physical inactivity, B12 deficiency, hearing impairment, low education and sleep disorders have also been linked with cognitive decline in the general population. With regard to depression itself, later age of first onset has been associated with cognitive impairment² and we have previously found that depression which has been active within the last 2 years is associated with greater risk of conversion from MCI to Alzheimer's dementia than a more remote history of depression. It is not known to what extent these risk factors may account for increased risk of MCI in adults with depression and normal cognition at baseline.

To the best of our knowledge, no study to date has been able to examine these questions in a large clinical sample of older adults attending specialist services using standardized diagnostic processes. The objectives of this study were to determine the overall proportion of older adults with depression who develop MCI during follow up and to identify

potentially modifiable risk factors which, if addressed could reduce risk of cognitive decline in this vulnerable population. We hypothesized that development of MCI would be associated with vascular risk factors, recently active depression and greater severity of depression

Methods

Study Sample

The National Alzheimer's Coordinating Centre (NACC) database includes data collected annually at participating Alzheimer's Disease Centres (ADCs) across the US. The database is maintained in the department of epidemiology at the University of Washington <https://www.alz.washington.edu/index.html>. Participants provide responses to psychological and cognitive questionnaires and may have a physical examination. Participants may voluntarily provide imaging and laboratory specimens at some of the participating ADCs. A Uniform Dataset (UDS) was implemented in September 2005 to prospectively gather standardized information from study participants. The UDS is not an epidemiologic sample and is best considered as a case series. This analysis is based upon a subsample of study participants from the UDS who attended from September 2005 through to September 2017. We included participants who had depression at baseline with normal cognition and attended for assessment on at least two occasions ($n = 2739$). We restricted our analysis to those aged 50 years and over at baseline ($n = 2655$) for consistency with previous longitudinal studies that have demonstrated increased risk of AD in late life depression. Written informed consents were obtained from participants at each ADC and approved by the ADC's Institutional Review Board (IRB). Research using the NACC database was approved by the University of Washington IRB.

Depression

Depression was defined as either (1) depression within the last two years or prior to two years as reported by the study participant to the assessing clinician at the initial visit (UDS Form A5) or (2) as clinician-reported depression at time of initial assessment according to DSM criteria at the time (UDS Form D1). The subject health history (Form A5) is completed by a "clinician, based on subject/informant report, medical records, and/or observation" using the clinician's best judgment. A history of depression is documented as present, absent or unknown with instructions to "include depressive disorders for which a clinician was consulted, whether or not treatment (behavioral or drug) was received. Depression includes major depressive disorder and other depressive syndromes for which a clinician was consulted. Assessment can include DSM diagnoses, chart reviews, clinicians' opinion, or whether the subject is taking an SSRI for a depressive/mood disorder." This definition of "clinically defined" depression is broadly based on DSM criteria, as that is the typical training for clinicians. Individuals with depression were also asked if they had "depression requiring medical attention within the last two years." Severity of depressive symptoms was assessed with the 15-item Geriatric Depression Scale (GDS).

Cognition & Dementia

Diagnostic assessments were made by a consensus team or the physician conducting the examination using a structured clinical history, neuropsychological testing and validated assessments of symptoms & function. Normal cognition was defined as having a global CDR score of zero and cognitive testing within normal limits. MCI was defined by the presence of cognitive complaint with cognitive decline not normal for age and maintained functional activities. A dementia syndrome was diagnosed according to DSM IV criteria and dementia diagnoses were made by a consensus team or the physician conducting the examination using the a structured clinical history, neuropsychological testing and Clinical Dementia Rating (CDR) form. Alzheimer's dementia was diagnosed according to NINCDS/ADRDA criteria prior to 2015 and according to NIA-AA criteria from 2015 onwards when the UDS was updated (version 3). Total Mini Mental Status Examination (MMSE) score (using WORLD) was completed on study participants (versions 1–2) at baseline.

Medical conditions & health behaviors

A list of common medical conditions was collected using a structured health history form (form A5). The form was completed by a clinician based on participant report, medical records and/or observation. A medical condition was considered to present if it was active within the last year or occurred in the past. We included medical conditions known to be associated with both depression and increased risk of cognitive decline including: hypertension, hypercholesterolemia, diabetes, atrial fibrillation, previous heart attack/arrest, previous stroke or TIA or B12 deficiency. Participants were also asked whether they had a history of alcohol abuse (defined as significant impairment occurring over a 12 month period in one of the following areas: work, driving legal or social) and for how many years they had smoked cigarettes.

Physical Examination

The majority of participants had a brief physical examination by the study clinician who recorded whether there was hearing impairment (without hearing aid) or visual impairment (without corrective lenses). A proportion of participants had genetic testing which usually consisted of either a blood test or a buccal swab according to ADC centre but could also be obtained at autopsy. It was determined whether participants were either homozygous or heterozygous for the e4 allele associated with increased risk of AD.

Antidepressant medication

A general antidepressant variable is included in the NACC dataset. This variable includes antidepressant medications from different classes including: SSRI, tricyclic, monoamine oxidase inhibitor, phenylpiperazine, tetracyclic, and serotonin–norepinephrine reuptake inhibitors. This variable allows for a group level analysis of antidepressant medications but does not allow for analysis of individual antidepressant classes.

Analyses

We conducted baseline descriptive analyses according to subsequent progression to MCI or not among older adults with depression. To determine which variables were associated with

increased risk of developing MCI we then conducted survival analyses. In a survival analysis the main outcome is time to the occurrence of an event of interest. In this case the event of interest was development of MCI (defined as first diagnosis of MCI, or where MCI was not diagnosed, first diagnosis of dementia during follow up). Survival analysis is frequently used to analyze longitudinal data of this type where time to the event of interest and duration of follow up varies between participants. We used Cox proportional hazards regression models (a type of survival model) that allowed us to adjust for the effects of other covariates on risk of AD. The measure of effect (potential for an event to occur during the follow up period) is presented as a hazard ratio. A Hazard Ratio (HR) > 1 indicates increased risk while HR < 1 indicates reduced risk for each predictor variable. Censoring was used to account for participants who did not receive a diagnosis of MCI or dementia during follow up & who left the study. Variables significantly associated with AD in bivariate survival analyses were selected for a multivariable Cox proportional hazards regression model. Prior to running the final model, the variables were assessed for multicollinearity using tolerance statistics (tolerance < 0.4 as a cut-point) to avoid unstable estimates of effect. The assumption of proportionality was examined to ensure that the Cox proportional hazards assumption was met. All analyses were conducted utilizing Stata 12.1 for mac. A p value < 0.05 was considered statistically significant.

Results

2655 study participants with normal cognition and clinically defined depression were included in the baseline analysis. 1935 (72.9%) were female with a mean age of 70.1 (SD 9.1). 586 (22.1%) developed either MCI ($n = 509$, 19.2%) or dementia ($n = 77$, 2.9%) over a median follow up duration of 41.8 months (range 8 – 139). Clinical characteristics of study participants at baseline according to subsequent development of MCI (or dementia where MCI was not diagnosed) during follow up are summarized in table 1.

Survival analyses

In bivariate survival analyses the baseline clinical characteristics of age (HR 1.07, 95% CI 1.06 – 1.08), female sex (HR 0.66, 95% CI 0.56 – 0.78), education (HR 0.93, 95% CI 0.91 – 0.96) & baseline MMSE (HR 0.79, 95% CI 0.75 – 0.83) were significantly associated with development of MCI or dementia. In addition several vascular risk factors, B12 deficiency and hearing impairment were associated with increased risk and results are presented in table 2. All clinical characteristics significantly associated with increased risk of MCI or dementia in bivariate analyses from table 2 were then assessed for multicollinearity and entered into a Cox proportional hazards regression model to determine which variables would remain independently associated with cognitive decline. We found that age 1.07 (1.05 – 1.08), female sex 0.72 (0.59 – 0.88), education 0.96 (0.93 – 0.99) baseline MMSE 0.87 (0.82 – 0.93), active depression within the last 2 years 1.41 (1.15 – 1.74) and severity of depressive symptoms 1.05 (1.02 – 1.09) remained significantly associated with development of MCI or dementia (table 3).

Discussion

In this analysis we found that 22% of older adults with depression and normal cognition at baseline developed either MCI or dementia over a median follow up duration of 42 months. In a previous longitudinal analysis in this dataset, not specifically focused upon older adults with depression, 6.2% developed MCI each year over a mean follow up duration of 2.7 years. We have previously reported that once MCI had become established in older adults with depression that approximately 40% progressed to Alzheimer's dementia over a median follow up of 27 months. This represents a very high proportion of older adults with depression who unfortunately continued to decline despite regular attendance at specialized memory services. It seems likely, therefore that if we are to substantially reduce the incidence of dementia in older adults with depression, there must be a greater focus upon maintaining cognitive health and *preventing MCI* in older adults with depression.

We found significant independent relationships between severity of depression, recency of depression (active depression within the last two years) and increased risk of MCI. For each additional point on the GDS scale of depression severity we observed a 5 – 10% increased risk of subsequent MCI (adjusted & unadjusted values respectively). Increasing severity of depressive symptoms has previously been associated with accelerated cognitive decline.¹ This raises the possibility that more effective management of depression could prevent cognitive decline either through behavioral changes such as increased physical activation or through correction of underlying patho-physiological mechanisms such as inflammatory activation, hypercortisolemia or increased oxidative & nitrosative stress. We did not find a significant relationship between antidepressant use and incident MCI in this analysis but note that a previous larger analysis reported a protective effect for antidepressant medication and subsequent diagnosis of dementia over a longer duration of follow up. It has been proposed that antidepressants may exert neuroprotective effects by increasing trophic factors or reducing accumulation of beta-amyloid.² We also found that having active depression within the last 2 years was associated with increased risk compared to having a more remote history of depression. Depression with both early and late onset has been associated with increased risk of cognitive decline.³ Individuals with recently active depression could include those with both early onset persistent/recurrent depression and those with late onset depression. It is not possible to more definitively determine the direction of causation here as we did not have data regarding age of first depressive episode or total number & severity of previous depressive episodes to address this question in greater detail. Depression with first onset in later years could represent an early symptom of Alzheimer's pathology. This proposition is supported by the association between beta-amyloid and tau pathology and depression in molecular neuroimaging studies of adults with normal cognition.⁴ It has also been proposed that depression is a true risk factor which, if adequately addressed, could lead to substantial reductions in new cases of dementia. Depression may accelerate cognitive decline via behavioral changes such as physical inactivity and is known to have a bidirectional relationship with cerebrovascular disease.⁵ Once depression is established, associated physiologic changes such as inflammation, hypercortisolemia, increased oxidative stress and reduced trophic factors could further compound neuronal compromise.⁶

These pathways are not mutually exclusive and could have shared causes or facilitate clinical expression of each other by diminishing cognitive reserve.

Consistent with findings in the general population, we found that higher education & baseline cognition exerted a protective effect against incident MCI. We also found a reduced risk of MCI in female study participants. This is consistent with a number of previous studies that have reported a greater risk of MCI, particularly non-amnesic MCI, in males. Females have been observed to have accelerated cognitive decline once MCI has become established potentially accounting, in part at least, for overall higher prevalence of Alzheimer's dementia observed in females.

We found that several vascular risk factors including hypercholesterolemia, hypertension, smoking and diabetes were associated with increased risk of MCI in bivariate analyses in addition to atrial fibrillation, previous myocardial infarction and cerebrovascular disease. These findings are in line with those in the previous analyses with increasing risk described as risk factors accumulate. Atrial fibrillation has previously been associated with increased risk of dementia and anticoagulants hold potential to prevent cognitive decline by reducing cerebral exposure to silent microemboli. We also found an association between a history of B12 deficiency and incident MCI. The relationship between B12 and cognitive decline could be mediated by elevated homocysteine which has been associated with increased risk of cognitive decline in several longitudinal studies. We also found that hearing impairment was associated with increased risk of MCI and this has been increasingly recognized as an important risk factor for cognitive decline. The variables listed above did not remain independently associated with MCI in a multivariable survival analysis likely reflecting adjustment for baseline cognition, the short duration of follow up and potentially improved management given that all participants were attending specialist memory services. Data from interventional studies to reduce risk of cognitive decline in the general population remain limited with some evidence to support treatment of hypertension, increasing physical activity, cognitive training and Mediterranean diet. While definitive evidence is still lacking, our findings lend some support for the proposition that effective management of depression and addressing modifiable risk factors for cognitive decline could reduce risk of MCI in older adults with depression over the longer term.

This study has a number of strengths and limitations. Strengths include the ability to examine several variables in this large dataset of individuals who underwent standardized assessments in specialist memory services. Depression was not defined by diagnostic interview although was based on information provided in the course of a standardized assessment to specialist clinicians familiar with diagnosis and assessment of depression. The duration of follow up is relatively short and it is likely that individuals developed MCI beyond the timeframe captured here. We did not have data regarding other modifiable variables such as physical activity. Finally, this dataset is best considered as a case series of individuals attending specialist services and may not be generalized to the overall community dwelling population.

In conclusion, we found that the development of MCI was associated with several potentially modifiable variables in older adults with depression. The high rate of progression

to dementia once MCI has become established necessitates a greater focus upon prevention of MCI if we are to substantially reduce the incidence of dementia in older adults with depression. Future studies should explore whether active management of risk factors could reduce incidence of MCI in this vulnerable population.

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Clinical Points

- Depression is associated with a two-fold risk of dementia and up to 40% of older adults with depression and MCI develop dementia despite attending specialist centers. We must focus upon *prevention of MCI* if we are to meaningfully reduce risk of dementia in older adults with depression
- While definitive evidence is still lacking our findings suggest that effective management of depression and addressing modifiable risk factors for cognitive decline could reduce risk of MCI in older adults with depression over the longer term.

Table 1:

Descriptive analyses of study participants at baseline according to subsequent progression to MCI (Mild Cognitive Impairment) or not (t test for continuous & χ^2 test for categorical variables).

	MCI (n = 586)	No MCI (n = 2069)	t/χ^2	P
Age (mean yrs, SD)	75.1 (8.6)	68.7 (8.7)	-15.9	< 0.001
Sex (female, %)	385 (65.7)	1550 (74.9)	19.6	<0.001
Education (mean yrs, SD)	15.3 (3.2)	15.9 (2.9)	4.5	< 0.001
MMSE score (mean, SD)	28.6 (1.5)	29.1 (1.2)	7.9	< 0.001
Depression				
Active in last 2yrs (yes, %)	423 (72.4)	1303 (63.2)	17.0	< 0.001
Severity (GDS, mean, SD)	2.87 (2.9)	2.20 (2.7)	-5.11	< 0.001
Antidepressant (yes, %)	276 (48.4)	1015 (49.4)	0.19	0.667
Medical conditions present				
Hypertension	315 (54.0)	992 (48.1)	6.4	0.012
Hypercholesterolemia	320 (55.5)	1050 (51.3)	3.1	0.081
Diabetes	88 (15.0)	255 (12.4)	2.9	0.091
Atrial fibrillation	50 (8.6)	99 (4.8)	12.4	< 0.001
Heart attack/arrest	45 (7.7)	81 (3.9)	14.3	< 0.001
Stroke/TIA	55 (9.5)	121 (5.9)	9.4	0.002
B12 Deficiency	35 (6.1)	91 (4.5)	2.6	0.105
Sleep disturbance	90 (16.9)	285 (14.6)	1.8	0.183
Health Behaviors				
Smoking (mean yrs,SD)	12.2 (16.9)	10.9 (15.1)	-1.8	0.076
Alcohol abuse (ever, %)	28 (4.8)	122 (5.9)	10.7	0.301
Physical examination				
Hearing impairment (yes,%)	158 (28.0)	350 (17.2)	33.2	< 0.001
Visual impairment (yes, %)	369 (65.4)	1436 (70.5)	5.27	0.022
APOE (e4 allele present, %)	173 (33.4)	541 (29.9)	2.29	0.131

Table 2:

Hazard Ratios for development of MCI (Mild Cognitive Impairment) for each predictor variable in unadjusted bivariate survival analyses

Predictor variable	Analytic Sample size	Hazard ratio (95% CI)
Age (total yrs)	2655	1.07 (1.06 – 1.08) **
Sex (female sex)	2655	0.66 (0.56 – 0.78) **
Education (total yrs)	2645	0.93 (0.91 – 0.96) **
MMSE (total score)	2481	0.79 (0.75 – 0.83) **
Depression		
Active in last 2yrs (yes)	2645	1.48 (1.23 – 1.77) **
Severity (total GDS score)	2563	1.10 (1.07 – 1.13) **
Antidepressant (yes)	2623	1.06 (0.89 – 1.24)
Medical Conditions Present		
Hypertension	2645	1.31 (1.12 – 1.55) *
Hypercholesterolemia	2622	1.23 (1.05 – 1.45) *
Diabetes	2644	1.37 (1.09 – 1.72) *
Heart attack/arrest	2649	2.02 (1.49 – 2.73) **
Atrial fibrillation	2636	1.82 (1.36 – 2.43) **
Stroke/TIA	2634	1.65 (1.25 – 2.18) **
B12 Deficiency	2606	1.59 (1.14 – 2.25) *
Sleep disturbance	2481	1.24 (0.99 – 1.55)
Health Behaviors		
Smoking (total yrs)	2602	1.006 (1.001 – 1.01) *
Alcohol abuse (ever in past)	2651	0.79 (0.54 – 1.16)
Physical examination		
Hearing impairment (yes)	2604	1.67 (1.39 – 2.01) **
Visual impairment (yes)	2602	0.88 (0.74 – 1.04)
APOE (e4 allele) present	2326	1.13 (0.94 – 1.35)

* Statistical significance at $p < 0.05$

** $p < 0.001$

Table 3:

Final multivariable survival analysis presenting significant independent predictors for development of MCI (Mild Cognitive Impairment).

Predictor variable	Hazard ratio (95% CI)
Age (total yrs)	1.07 (1.05 – 1.08) **
Sex (female sex)	0.72 (0.59 – 0.88) *
MMSE (total score)	0.87 (0.82 – 0.93) **
Education (total yrs)	0.96 (0.93 – 0.99) *
Depression active in last 2yrs (yes)	1.41 (1.15 – 1.74) *
Depression severity (total GDS score)	1.05 (1.02 – 1.09) *

* Statistical significance at $p < 0.05$

** $p < 0.001$