# Obsessive-Compulsive Disorder and Dementia Risk:
## A Nationwide Longitudinal Study

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**ABSTRACT**

***Background:*** Several case reports have suggested an association between obsessive-compulsive disorder (OCD) and dementia. However, the exact relationship remains unclear.

***Methods:*** Using the Taiwan National Health Insurance Research Database, 1,347 patients with OCD (*ICD-9-CM* code 300.3) aged ≥ 45 years and 13,470 controls matched for age, sex, residence, income, and dementia-related comorbidities were included between 1996 and 2013 for investigation of subsequent dementia from enrollment to the end of 2013. Stratified Cox regression analysis on each matched pair was applied to assess the dementia risk between the OCD and control groups. The analysis for the current study was performed in 2018.

***Results:*** Patients with OCD had increased risk of developing any dementia (hazard ratio [HR] = 4.28; 95% confidence interval [CI], 2.96–6.21), Alzheimer's disease (HR = 4.04; 95% CI, 1.55–10.54), and vascular dementia (HR = 3.95; 95% CI, 1.70–9.18) compared with controls.

***Discussion:*** Future research on the pathogenic mechanisms and molecular underpinnings of the relationship between OCD and dementia may lead to the development of novel therapeutics.

*J Clin Psychiatry 2021;82(3):20m13644*

***To cite:*** Chen MH, Cheng CH, Tsai SJ, et al. Obsessive–compulsive disorder and dementia risk: a nationwide longitudinal study. *J Clin Psychiatry.* 2021;82(3):20m13644.

***To share:*** https://doi.org/10.4088/JCP.20m13644



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Obsessive-compulsive disorder (OCD) is a severe, chronic mental disorder that affects 1%–2% of the population at some point in their lives. It manifests as intrusive troubling thoughts (obsessions) and repetitive ritualistic behaviors (compulsions) that are time consuming, significantly impair functioning, and cause distress.[1,2] The World Health Organization ranks OCD among the most disabling conditions worldwide: the 4th in the age group of 15–49 years, 10th in the age group of 50–69 years, and 20th in the age group of ≥ 70 years. Disability-adjusted life-years attributable to anxiety disorders, including OCD, have increased by up to 40% in recent decades.[3,4]

Increasing evidence has indicated a relationship between OCD and dementia-related risk factors, such as type 2 diabetes mellitus and cerebrovascular diseases.[5–7] Albert et al[7] examined metabolic syndrome among 104 patients with OCD and found that hypertension was present in 42.3%, high triglycerides in 23.1%, low high-density lipoprotein cholesterol in 22.1%, and fasting hyperglycemia in 4.8%. In their assessment of metabolic and cerebrocardiovascular complications in patients with OCD in Sweden, Isomura et al[5] demonstrated that patients with OCD had higher risks of type 2 diabetes mellitus (hazard ratio [HR] = 1.22; 95% confidence interval [CI], 1.13–1.31) and circulatory system diseases (HR = 1.44; 95% CI, 1.41–1.48) compared with controls. A genome-wide association study[6] found a shared genetic etiology between type 2 diabetes mellitus and contamination OCD and further indicated that fasting insulin levels exhibited genetic sharing with OCD.

In the 2000s, some evidence suggested a potential link between OCD and dementia, especially Alzheimer's disease.[8,9] Dondu et al[8] assessed the obsessive-compulsive symptoms (OCSs) between patients with Alzheimer's disease and controls and found that lifetime and current OCSs were significantly more prevalent in patients with Alzheimer's disease than in controls. Mrabet et al[9] reported a case of a 75-year-old woman who had had severe OCD with contamination obsessions and washing compulsions since the age of 45 years. She had developed progressive symptoms of memory decline, disorientation in place and time, object misplacement, and word-finding difficulties starting from the age of 68 years, when she had been diagnosed as having Alzheimer's disease and had begun donepezil treatment after a comprehensive dementia survey. Notably, her family had a strong history of OCD (sisters and cousin) and of dementia (her father and other sisters).[9] The association between OCD and dementia remains a topic rarely investigated, and past studies have been significantly confounded by small sample sizes and retrospective case-control designs.

We used the Taiwan National Health Insurance Research Database (NHIRD) to form the participant pool. This large-scale longitudinal study investigated the risk of developing any dementia, Alzheimer's disease, and vascular dementia among patients with OCD. We hypothesized that OCD was an independent risk factor for subsequent dementia,

**Clinical Points**

- Obsessive-compulsive disorder (OCD) was an independent risk factor for subsequent dementia, including Alzheimer's disease and vascular dementia.
- Regular assessments for memory and cognitive function may be suggested for elderly individuals with OCD to ensure early detection and timely medical care.

Alzheimer's disease, and vascular dementia, regardless of dementia-related comorbidities such as diabetes or other demographic characteristics such as socioeconomic status.

## METHODS

### Data Source

The Taiwan National Health Insurance (NHI) program is a universal single-payer system providing compulsory health insurance to all residents of Taiwan and was initiated in 1995. At the end of 2010, approximately 99.6% of the 23 million Taiwanese residents received medical coverage through this program. Established for research purposes and audited by the Department of Health and the Bureau of the NHI program, the NHIRD contains comprehensive information about the insured patients, such as demographics (birthdate, sex, residential location, income status) and clinical visits (dates and diagnoses). To protect privacy, each patient is assigned a unique and anonymous identifier upon enrollment by the NHI, which allows researchers to follow their diseases and outcomes. Diagnoses were captured using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). The NHIRD has been used extensively for epidemiologic studies.[10–15] This study was approved by the Taipei Veterans General Hospital Institutional Review Board. The analysis for the current study was performed in 2018.

### Inclusion Criteria for Patients With OCD and Matched Controls

Adults ≥45 years old who were diagnosed with OCD (*ICD-9-CM* code 300.3) by board-certified psychiatrists at least twice between January 1, 1996, and December 31, 2013, and who had no dementia history before their OCD diagnoses were included in the OCD cohort. Exact matching was used to match this cohort in a 1:10 fashion to controls without diagnoses of either dementia or OCD and other psychiatric disorders (*ICD-9-CM* codes 295, 296, 297, and 300) prior to the enrollment for other medical causes on the bases of age (± 1 year), sex, enrollment time, dementia-related medical comorbidities, income level (levels 1–3 per month: ≤ 15,840 NTD [new Taiwanese dollars] or 528 USD [US Dollars], 15,841–25,000 NTD or 528–833 USD, and ≥ 25,001 NTD or ≥ 833 USD), and urbanization level of residence (levels 1–5, most to least urbanized), a proxy for health care availability in Taiwan.[16] Dementia-related comorbidities included history of cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidemia, diabetes mellitus, and smoking. Additionally, Charlson Comorbidity Index (CCI) scores and all-cause clinical visits were ascertained for the OCD and the matched-control cohorts. CCI consisting of 22 physical conditions was administered to determine the systemic health conditions of all enrolled subjects.[17] All-cause clinical visits (the numbers of clinical visits per year) for the OCD cohort and the matched-controls cohort were included as a variable to account for potential detection bias.

### Outcome Assessment

Diagnosis of dementia (*ICD-9-CM* codes 290.0 [senile dementia, uncomplicated], 290.1 [presenile dementia], 290.2 [senile dementia with delusional or depressive features], 290.3 [senile dementia with delirium], 290.4 [vascular dementia], 294.1 [dementia in conditions classified elsewhere], 294.2 [dementia, unspecified], 331.0 [Alzheimer's disease], 331.1 [frontotemporal dementia], 331.2 [senile degeneration of brain], and 331.82 [dementia with lewy bodies]) was documented at least twice by board-certified psychiatrists or neurologists during the follow-up period (from enrollment to December 31, 2013, or death). The mean ± SD interval of 2 diagnosis documentations was 87.93 ± 300.68 days. Alzheimer's disease was either defined by the specific *ICD-9-CM* code of 331.0 or identified by *ICD-9-CM* codes for dementia (290.0, 290.1, 290.2, 290.3, 290.4, 294.1, and 294.2) while the individual was also receiving medications for dementia. On the basis of the NHI regulations, reimbursable therapies for dementia (ie, cholinesterase inhibitors) were approved only after comprehensive laboratory and imaging examinations to exclude cognitive decline from other causes, including thyroid dysfunction, vitamin $B_{12}$ deficiency, or cerebrovascular events; medications were not approved for Alzheimer's disease with any evidence of cerebrovascular lesions. Furthermore, vascular dementia was defined by the specific *ICD-9-CM* code of 290.4. Other types of dementia, especially Alzheimer's disease with evidence of any cerebrovascular lesion, were defined as unspecified dementia in our study because the definite dementia pathology cannot be clearly defined based on the *ICD-9-CM* codes 290.0, 290.1, 290.2, 290.3, 290.4, 294.1, and 294.2 alone without concurrent medication prescription for Alzheimer's disease, reflecting the clinical practice in Taiwan. For this reason, Alzheimer's disease with cerebrovascular lesions was defined as unspecified dementia, and the diagnostic validity of Alzheimer's disease as the sole reason for neurocognitive degeneration is high. Finally, early-onset dementia was defined as dementia with age at onset < 65 years.

### Statistical Analysis

For between-group comparisons, the *F* test was used for continuous variables (mean, standard deviation) and the Pearson $\chi^2$ test for nominal variables. Stratified Cox regression analysis on each matched pair (the patient and their 10 matched controls in a 1:10 fashion) with

adjustment for age, CCI score, and all-cause clinical visits was applied to investigate the dementia risk between the OCD and control groups. Subanalyses stratified by sex were performed. Given the insidious onset of dementia, two types of sensitivity analyses were performed to validate the results by minimizing underdiagnosis of occult dementia at the time of OCD diagnosis. In the "exclusion of observation period" model, the first 3 or 5 years of observation after the OCD diagnosis were excluded, eliminating all cases of dementia diagnosed within these first years following OCD diagnosis. For example, in the "exclusion of the first 3-year observation period" model, the diagnosis of dementia following OCD diagnosis within 3 years was censored, but was not regarded as the event. In the "exclusion of enrollment period" model, only patients diagnosed with OCD after the dates January 1, 2000, or January 1, 2005, were included in the analysis; patients with OCD diagnosed prior to these time points were selectively excluded. For example, a patient diagnosed on January 1, 2003, would be included in the "exclusion of enrollment period" model of the dates after January 1, 2000, but was excluded in the "exclusion of enrollment period" model of the dates after January 1, 2005. Statistical significance was set at 2-tailed $P \leq .05$. Data processing and statistical analyses were performed with SAS (version 9.1; SAS Institute; Cary, NC).

**Table 1. Demographic Data and Incidence of Dementia Among Patients With OCD and the Control Group[a]**

| Variable | Patients with OCD (n = 1,347) | Controls (n = 13,470) | *P* value |
|---|---|---|---|
| Age at enrollment, mean (SD), y | 55.77 (8.63) | 55.72 (8.67) | .839 |
| Sex | | | 1.000 |
| Male | 597 (44.3) | 5,970 (44.3) | |
| Female | 750 (55.7) | 7,500 (55.7) | |
| Dementia-related comorbidity | | | |
| Cerebrovascular diseases | 194 (14.4) | 1,940 (14.4) | .997 |
| Traumatic brain injury | 59 (4.4) | 590 (4.4) | .993 |
| Hypertension | 577 (42.8) | 5,770 (42.8) | 1.000 |
| Dyslipidemia | 287 (21.3) | 2,870 (21.3) | .998 |
| Diabetes mellitus | 449 (33.3) | 4,490 (33.3) | .999 |
| Smoking | 39 (2.9) | 390 (2.9) | .991 |
| CCI score, mean (SD) | 2.80 (2.30) | 1.95 (2.04) | < .001 |
| Level of urbanization | | | 1.000 |
| 1 (most urbanized) | 175 (13.0) | 1,750 (13.0) | |
| 2 | 265 (19.7) | 2,650 (19.7) | |
| 3 | 81 (6.0) | 810 (6.0) | |
| 4 | 127 (9.4) | 1,270 (9.4) | |
| 5 (most rural) | 699 (51.9) | 6,990 (51.9) | |
| Income-related insured amount | | | 1.000 |
| ≤ 15,840 NTD/mo | 518 (38.5) | 5,180 (38.5) | |
| 15,841–25,000 NTD/mo | 499 (37.0) | 4,990 (37.0) | |
| ≥ 25,001 NTD/mo | 330 (24.5) | 3,300 (24.5) | |
| Incidence of any dementia | 87 (6.5) | 124 (0.9) | < .001 |
| Incidence of any early-onset dementia[b] | 23 (1.7) | 9 (0.1) | < .001 |
| Age at diagnosis of any dementia, mean (SD), y | 70.52 (9.19) | 76.73 (7.23) | < .001 |
| Duration between enrollment and dementia, mean (SD), y | 3.74 (3.29) | 7.50 (4.01) | < .001 |
| Dementia type | | | |
| Alzheimer's disease | 23 (1.7) | 20 (0.1) | < .001 |
| Vascular dementia | 15 (1.1) | 30 (0.2) | < .001 |
| Unspecified | 49 (3.6) | 74 (0.5) | < .001 |
| All-cause clinical visits per year, mean (SD) | 24.18 (49.34) | 11.39 (11.53) | < .001 |

[a]Values shown as n (%) unless otherwise noted.
[b]Early onset dementia: 45–64 years.
Abbreviations: CCI = Charlson Comorbidity Index, OCD = obsessive-compulsive disorder, NTD = new Taiwan dollar.

### Data Availability Statement

The NHIRD was released and audited by the Department of Health and Bureau of the NHI Program for the purpose of scientific research (https://nhird.nhri.org.tw/). Access to the NHIRD can be obtained through the formal application that is regulated by the Department of Health and Bureau of the NHI Program.

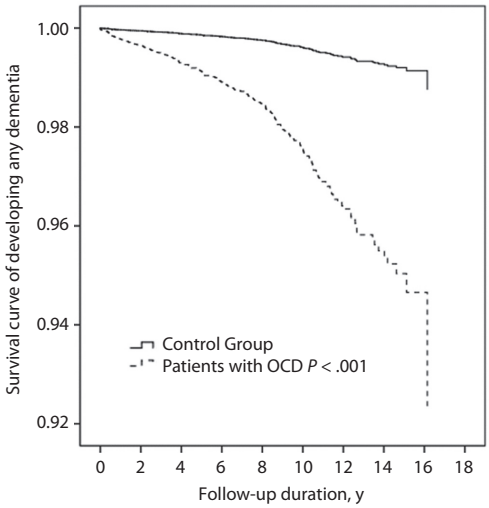
## RESULTS

In all, 1,347 patients with a mean ± SD age of 55.77 ± 8.63 years and with a diagnosis of OCD and 13,470 age-, sex-, residence-, income-, and comorbidities-matched controls were included in current study (Table 1). Patients with OCD were more likely to develop any dementia (6.5% vs 0.9%, $P < .001$), Alzheimer's disease (1.7% vs 0.1%, $P < .001$), vascular dementia (1.1% vs 0.2%, $P < .001$), and unspecified dementia (3.6% vs 0.5%, $P < .001$) than the control group (Table 1). In addition, the incidence of early-onset dementia significantly differed between OCD and control groups (1.7% vs 0.1%, $P < .001$) (Table 1). Patients with OCD had the higher mean ± SD CCI scores (2.80 ± 2.30 vs 1.95 ± 2.04, $P < .001$) and all-cause clinical visits per year (24.18 ± 49.34 vs 11.39 ± 11.53, $P < .001$) compared with controls (Table 1).

Kaplan-Meier survival analysis showed that patients with OCD had a significantly increased risk of dementia compared with the controls ($P < .001$) (Figure 1). Cox regression analysis stratified on each matched pair and with adjustment for age, CCI score, and all-cause clinical visits showed that patients with OCD had increased risks of developing any dementia (HR = 4.28; 95% CI, 2.96–6.21), Alzheimer's disease (HR = 4.04; 95% CI, 1.55–10.54), vascular dementia (HR = 3.95; 95% CI, 1.70–9.18), and unspecified dementia (HR = 4.57; 95% CI, 2.87–7.28) during the follow-up period compared with controls (Table 2). Subanalyses further found that OCD in male patients was related to Alzheimer's disease (HR = 6.43; 95% CI, 1.42–29.13) and that OCD in female patients was associated with vascular dementia (HR = 4.76; 95% CI, 1.54–14.74) (Table 2).

Finally, sensitivity analyses with both "exclusion of observation period" and "exclusion of enrollment period" models found the consistent findings that increased HRs of subsequent dementia after OCD diagnosis varied between

**Figure 1. Survival Curve of Developing Any Dementia Among Patients With OCD and the Control Group**




Abbreviation: OCD = obsessive-compulsive disorder.

**Table 2. Risk of Developing Dementia Among Patients With OCD and Controls[a,b]**

| OCD Presence vs Absence | Alzheimer's disease | Vascular dementia | Unspecified dementia | Total |
|---|---|---|---|---|
| Overall | **4.04 (1.55–10.54)** | **3.95 (1.70–9.18)** | **4.57 (2.87–7.28)** | **4.28 (2.96–6.21)** |
| Stratified by sex | | | | |
| Male with OCD | **6.43 (1.42–29.13)** | 3.76 (0.98–14.40) | **3.85 (1.96–7.58)** | **4.07 (2.35–7.03)** |
| Female with OCD | 2.87 (0.79–10.46) | **4.76 (1.54–14.74)** | **5.46 (2.84–10.50)** | **4.51 (2.72–7.50)** |

[a]Values are shown as hazard ratio (95% CI) as determined with Cox regression analysis stratified on each matched pair and with adjustment for age, CCI score, and all-cause clinical visits.
[b]Bold type indicates statistical significance.
Abbreviations: CCI = Charlson Comorbidity Index, OCD = obsessive-compulsive disorder.

**Table 3. Sensitivity Analyses of Developing any Dementia Among Patients With OCD and Controls[a,b]**

| | | Exclusion of Observation Period | | Exclusion of Enrollment Period | |
|---|---|---|---|---|---|
| Variable | Total | > 3 Years | > 5 Years | Enrollment Year ≥ 2000 | Enrollment Year ≥ 2005 |
| Presence of OCD | **4.28 (2.96–6.21)** | **3.97 (2.61–6.02)** | **3.04 (1.86–4.95)** | **4.31 (2.88–6.45)** | **5.30 (2.71–10.36)** |
| Absence of OCD | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |

[a]Values are shown as hazard ratio (95% CI) as determined with Cox regression analysis stratified on each matched pair and with adjustment for age, CCI score, and all-cause clinical visits.
[b]Bold type indicates statistical significance.
Abbreviations: CCI = Charlson Comorbidity Index, OCD = obsessive-compulsive disorder.

3.04 (95% CI, 1.86–4.95) and 5.30 (95% CI, 2.71–10.36) (Table 3).

## DISCUSSION

Our findings support the hypothesis that patients with OCD had increased risks of subsequent dementia, Alzheimer's disease, and vascular dementia during the follow-up period compared with controls. In addition, based on the definitions from the studies by Chen et al[18] and Azuero[19] investigating the size effect measured by HR, the HRs of OCD and subsequent dementia ranged between 3.85 and 6.43 in current study, indicating the medium-to-large size effect.

Several case reports and a small case-control study have suggested a positive relationship of OCD with subsequent dementia, especially Alzheimer's disease.[8,9,20] Frydman et al[20] reported a case of an elderly patient who exhibited late-onset and treatment-refractory OCD that developed into full-blown dementia after 7 years of follow-up. Roth et al[21] indicated that patients with late-onset OCD exhibited poorer executive function, visual memory, and auditory attention than those with early-onset OCD. Older age at onset of OCD was associated with worse performance on memory tasks, and low scores on memory tasks were associated with OCD severity.[22] A study of 39 patients with Alzheimer's disease and 30 age- and sex-matched controls[8] demonstrated that patients with Alzheimer's disease were more likely to have

current and lifetime hoarding and checking obsessions/compulsions compared with controls. Dondu et al[8] found that these symptoms appear to progress in dementia in contrast to other OCSs and suggested that the mean number of lifetime compulsions may predict Alzheimer's disease diagnosis, despite the fact that OCSs that developed prior to onset of Alzheimer's disease did not cause earlier onset of dementia or more severe cognitive impairment. Our findings are consistent with those observing a significant association between OCD and Alzheimer's disease. In addition, we found a relationship between OCD and vascular dementia, although studies have reported on the cerebrovascular burden, including stroke, among patients with OCD.[5,23] Furthermore, early-onset dementia was more prevalent in the OCD group than in the control group, suggesting that clinicians may want to monitor OCD patients to detect possible manifestations of early-onset dementia.[24]

Surprisingly, in contrast to past evidence that women are at greater risk of developing Alzheimer's disease and men are at greater risk of developing vascular dementia,[25] we found that male patients with OCD were more likely to develop Alzheimer's disease later in life and female patients with OCD were more likely to develop vascular dementia during the follow-up period compared with controls. A case-control study[26] revealed that male patients with OCD scored worse on nonverbal memory tasks than did controls, whereas the cognitive performance of women with OCD was consistent with that of their control counterparts. Potvin et al[27] found that elderly women with cognitive impairment no dementia (CIND) were more likely to have clinical (0.4% vs 0.0%) and subclinical (3.0% vs 1.9%) OCSs than elderly men with CIND. Studies have demonstrated that certain dementia-related risk factors, such as type 2 diabetes mellitus and hypertension, may adversely affect women more so than men.[28] Conversely, stroke, the leading risk factor for vascular dementia, has been found to have higher incidence in men than in women throughout most of the lifespan, although this trend is reversed at advanced ages.[25,28] Furthermore, indirect evidence has suggested that obsessive symptoms are associated with blunted cortisol awakening response, a potential biomarker for chronic stress and cerebrocardiovascular diseases, in women but not in men.[29,30] In the present study, after adjusting for hypertension, type 2 diabetes mellitus, hypertension, and cerebrovascular diseases, OCD was found to be an independent risk factor for vascular dementia among female, but not male, patients. Further studies are warranted to elucidate the definitive role of sex in the association of OCD with Alzheimer's disease and vascular dementia.

We propose several underlying mechanisms to explain the relationship between OCD and dementia. First, OCD and dementia may share a common genetic background.[9] Mrabet Khiari et al[9] genotyped a family comprising 3 patients who developed OCD before developing dementia, 9 with OCD alone, and 3 with dementia alone. The researchers suggested that glutamate system–related genes, including *SLC1A1* and *GRIN2B*, may play important roles in the pathophysiology of OCD and dementia, especially that of Alzheimer's disease.[9,31–33] Second, results from a proteomic study on the serum proteome profiles of patients with OCD[34] indicated that the protein–protein interaction network of OCD involves apolipoprotein A-4, haptoglobin,, complement component 3, albumin, amyloid precursor protein, and $\alpha_1$-antitrypsin. Those proteins were found to be involved in the acute phase response to inflammation, the hydrogen peroxide catabolic process, and the regulation of triglyceride metabolism and were associated with dementia pathophysiology.[34] In addition, Zamanian-Azodi et al[34] reported that serum transthyretin, a ligand that interacts with β-amyloid protein (Aβ) and disrupts Aβ fibrils, is a potential biomarker for OCD. Tien et al[35] and Azodi et al[36] demonstrated a temporal relationship between serum transthyretin level and the conversion from mild cognitive impairment to Alzheimer's disease. Furthermore, evidence of a relationship between OCD and metabolic and cerebrovascular diseases is increasing.[5,23] Vascular dementia may be indirectly associated with OCD-related dementia risk factors such as type 2 diabetes mellitus and cerebrovascular diseases.

Our study limitations reflect those of other registry-based studies. First, the incidence of dementia and the prevalence of OCD were potentially underestimated. Our study design maximized diagnostic validity by considering only diagnoses made by board-certified physicians. Diagnoses and coding were highly reliable because they are mandated by the Taiwanese government for medical reimbursement.[37] Therefore, the "unspecified" type of dementia in our analysis likely reflected patients with dementia who did not receive prescriptions, such as those with Alzheimer's disease with evidence of any cerebrovascular lesion and frontotemporal dementia. In addition, the association of OCD and frontotemporal dementia may need further investigation since the overlaps may be observed between OCD and frontotemporal dementia.[24] Second, despite the strong unidirectional association observed between OCD and subsequent dementia development, a causal relationship cannot be inferred. Finally, information on family history, environmental factors, lifestyle, and other factors was not available in the database we used.

In conclusion, we found that OCD was an independent risk factor for subsequent dementia. Average age at onset in patients was 6 years younger than the average age of matched controls. For elderly patients with OCD, undergoing regular assessments for memory and cognitive function, administered through a multidisciplinary approach, may be necessary to ensure early detection and timely medical care. Future research on the pathogenic mechanisms and molecular underpinnings of the relationship between OCD and dementia may lead to the development of novel therapeutics.

***Submitted:*** August 12, 2020; accepted November 30, 2020.
***Published online:*** May 11, 2021.
***Author contributions:*** Drs M-H Chen, Cheng, and Bai designed the study. Dr M-H Chen analyzed the data and drafted the first version of the manuscript.

Drs S-J Tsai, C-F Tsai, Su, Li, Lin, and T-J Chen performed the literature search. All authors contributed substantially to the manuscript and approved the final manuscript for submission. All authors are responsible for the integrity, accuracy, and presentation of the data.

***Potential conflicts of interest:*** None.

***Funding/support:*** The study was supported by grants from Taipei Veterans General Hospital (V106B-020, V107B-010, V107C-181, V108B-012), Yen Tjing Ling Medical Foundation (CI-109-21, CI-109-22, CI-110-30), and Ministry of Science and Technology (107-2314-B-075-063-MY3, 108-2314-B-075-037), Taiwan.

***Role of the sponsor:*** The funding sources had no role in any process of our study.

***Acknowledgments:*** The authors thank Mr I-Fan Hu, MA (Courtauld Institute of Art, University of London; National Taiwan University) for his friendship and support. Mr Hu declares no conflicts of interest.

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*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.